Neurology

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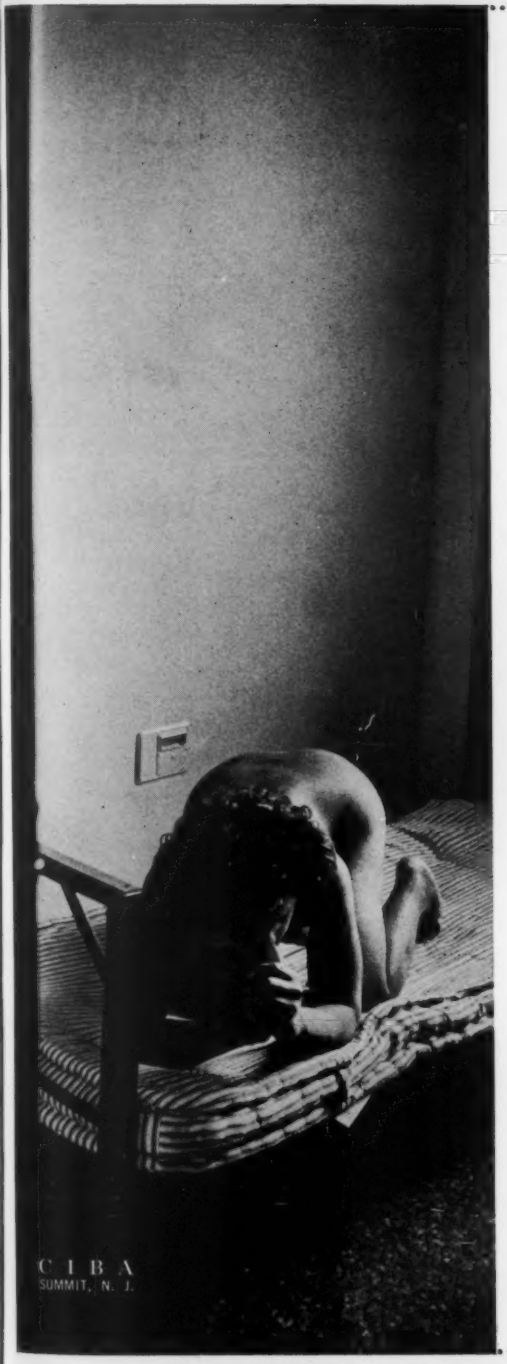

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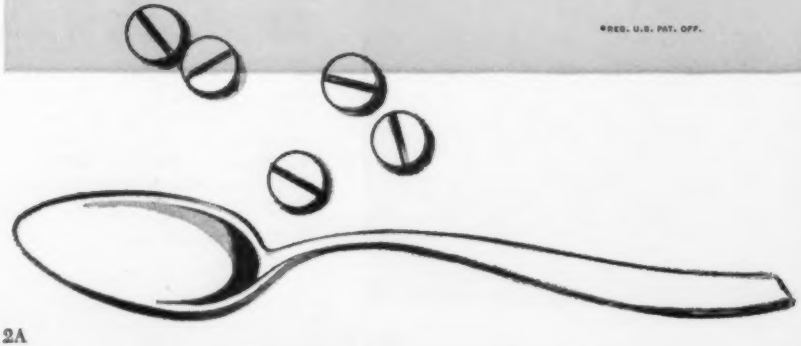

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FEBRUARY 1956 • *Contents*

Clinical Localization of Intracranial Aneurysms and Vascular Anomalies 79
A. EARL WALKER, M.D.

Myofascial Pain Syndromes 91
ANDERS E. SOLA, M.D. AND ROBERT L. WILLIAMS, M.D.

Craniovascular Studies in Headache
A Report and Analysis of Pulse Volume Tracings 96
PERCY BRAZIL, M.D. AND ARNOLD P. FRIEDMAN, M.D.

Metastatic Lesions of the Vertebral Column Causing Cord Compression 103
EBEN ALEXANDER, JR., M.D., COURTLAND H. DAVIS, JR., M.D. AND CHARLES H. FIELD, M.D.

Dystonic Amyotrophy
Dystonia and Muscular Atrophy 108
I. S. FREIMAN, M.D. AND J. LUWISCH, M.D.

Epilepsy and Dupuytren's Contracture 115
ALEX J. ARIEFF, M.D. AND JOHN BELL, M.D.

Swelling of the Brain Induced by Anoxia 118
RICARDO F. S. EDSTROM, M.D. AND HIRAM E. ESSEX, Ph.D.

(Continued on next page)

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Contents — *Continued*

Nature and Significance of Pentosuria in Neuromuscular Disease *(Concluded)* 125
DONALD B. TOWER, M.D., Ph.D., EDMUND L. PETERS, B.S. AND MILTON A. POGORELSKIN, B.S.

Diagnostic Note
Limited Value of Carotid Pulse in Diagnosis of Internal Carotid Thrombosis 143
HAROLD ROSEGAY, M.D.

Case Reports
Peripheral Neuropathy Associated with Multiple Myelomatosis 146
EDWIN CLARKE, M.D., M.R.C.P.

Ependymoma of the Cerebellopontine Angle in an Infant 152
JOSEPH G. CHUSID, M.D., C. G. DE GUTIERREZ-MAHONEY, M.D. AND THOMAS Q. GARVEY, JR., M.D.

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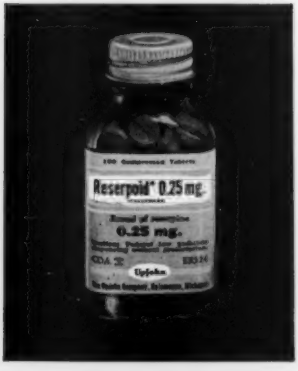

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Volume 6 Neurology Number 2

Clinical Localization of Intracranial Aneurysms and Vascular Anomalies

A. Earl Walker, M.D.

SUBARACHNOID HEMORRHAGE is now so readily recognized that the diagnosis can often be made on the basis of the history alone and confirmed by a simple lumbar puncture. Further management of the condition is not so easy for, although it is acknowledged that the most common causes of such bleeding are aneurysms and vascular anomalies, there are such differences in prognosis of the variously located aneurysms and the malformations that the ability to make an accurate localizing and pathologic diagnosis of the lesion is a great asset. But the clinical picture of the various aneurysmal tumors occurring in different parts of the brain has been neglected to a great extent as a result of the early statements that it was rarely possible to diagnose the position of a bleeding aneurysm during life.

Beadles,[1] in one of the earliest papers on aneurysms of the larger cerebral arteries, pointed out that aneurysms which present symptoms are in the minority and concluded that "the exact diagnosis of a cerebral aneurysm during life is no more possible today (1907) than it was when Gull wrote nearly 50 years ago."

Somewhat later Fearnsides[2] recognized that intracranial aneurysms form a definite nosologic group which should be capable of clinical diagnosis, but the subject was too confused for him to describe the syndromes related to aneurysms of various parts of the circle of Willis. Even Symonds[3] somewhat later considered that an aneurysm should be suspected when signs of an intracranial tumor at the base of the brain are associated with evidence of cerebral arteriosclerosis or infective endocarditis.

This account is an analysis of the clinical findings in a series of 285 aneurysmal tumors (aneurysms and vascular anomalies) in an attempt to indicate

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This work aided by a grant from the David S. Barry Fund.

some syndromes which might allow differential and localizing diagnoses.

A. ANEURYSMS

Although intracranial aneurysms may be of the inflammatory variety (mycotic), congenital or degenerative, this discussion will consider in detail only the latter types of aneurysmal tumors, and these collectively, since the mycotic aneurysms, of which there were six symptomatic and one asymptomatic in this series, are usually associated with sepsis in the vascular system and a fulminating fatal course. In this series the symptomatology was a hemiplegia followed within a few hours to several months by subarachnoid hemorrhage, coma, and death. In one case, a basilar aneurysm, such a syndrome did not occur, but coma supervened without a previous hemiparesis. For these reasons the diagnosis of a mycotic aneurysm is usually only of academic interest as a terminal event. But the recognition of the other types of aneurysmal tumors is of both prognostic and therapeutic value.

ANEURYSMS OF THE INTERNAL CAROTID ARTERY

Infraclinoid Aneurysms

The aneurysms of the internal carotid artery occurring below the anterior clinoid process lie almost entirely within the cavernous sinus. Their rupture produces a carotid-cavernous fistula, rarely epistaxis, and only subarachnoid hemorrhage should the lesion extend above the clinoid process.

In this series are six examples of unruptured infraclinoid aneurysms and another example of an aneurysm both above and below the anterior clinoid process. In five of the six cases the initial symptom of diplopia with or without ptosis was referable to the oculomotor nerves. In one case pain was the initial symptom and in two cases pain accompanied the diplopia. In the patient with a combined infra- and supraclinoid aneurysm unilateral blindness was the first manifestation. Hypertensive vascular disease was present in only one case and, as might be expected, subarachnoid hemorrhage only occurred in the patient with the supraclinoid extension.

Involvement of the cranial nerves was confined to the nerves within the cavernous sinus, and the second cranial nerve in two patients. The third cranial nerve was involved in all cases; the fourth in four cases, the sixth in five cases, and the first division of the fifth cranial nerve in two cases. The two patients with optic nerve involvement were blind in the involved eye. Such visual disturbances are not uncommon as the aneurysm enlarges and lifts up the optic nerve.

The clinical picture of the unruptured infraclinoid aneurysm is sufficiently typical that the diagnosis may be on the basis of the third nerve palsy with evidence of slight involvement of the upper one or two divisions of the trigeminal nerve. Occasionally exophthalmos may be present (25 per cent according to Dandy[4]).

Jefferson[5] divides the syndrome into: 1) Anterior cavernous syndrome (most common), in which the ophthalmic division of the trigeminal is only involved with the paresis of the oculomotor nerves. 2) Middle cavernous syndrome, in which the first two branches of the trigeminal are involved and the extraocular muscles paralyzed in whole or part. 3) Posterior cavernous syndrome, in which the entire trigeminal nerve is involved with some ocular palsy, at times only the abducens nerve. This division,

however, may be more academic than practical.

The above syndrome is not necessarily pathognomonic of an aneurysm, for other types of lesion in the same region may produce similar pictures. However, severe pain is somewhat more common with the infraclinoid aneurysms.

Rupture of this aneurysm into the cavernous sinus producing the typical picture of the carotid cavernous fistula is not very common. Rupture into the subarachnoid space, presumably through a supraclinoid extension, occurs rarely. Dandy[4] was able to collect four examples of this mishap in 35 cases of this type of aneurysm.

Carotid-cavernous fistula

The analysis of this syndrome is based upon a series of 24 cases.

Although rupture of an infraclinoid aneurysm does occur into the cavernous sinus, the majority of carotid-cavernous fistula (76.8 per cent according to Locke[6]) are of traumatic origin occurring immediately (30 per cent), in a week (30 per cent), or over a period of months after the injury. The bruit or noise in the head is usually the first manifestation and may be present for weeks before the exophthalmos becomes manifest. The latter is the cardinal symptom of a cavernous-carotid fistula. It is usually unilateral and in the ipsilateral eye. In approximately 10 per cent of cases it is bilateral (two of 24 cases in the series observed) and rarely occurs in the eye contralateral to the fistula. Very occasionally it may be absent, but it was present in all 24 cases of this series.

The next most common phenomenon is pulsation of the globe, present in almost 90 per cent of cases and associated often with a thrill on palpation of the orbit or the engorged vessels of the forehead. The bruit varies in intensity and degree of annoyance. Upon auscultation it is heard as a crescendo systolic murmur, usually most prominent over the eyeball and temporal region. It is usually diminished or abolished by compression of the ipsilateral carotid artery.

Extraocular palsies associated with carotid-cavernous fistula may result from the primary injury or be due to compression of the nerves in the sinus wall. Diplopia is usually due to abducens involvement (in the present series seen in two cases), but other nerves (in this series two complete ophthalmoplegias) may be damaged.

Impairment of vision is a frequent accompaniment of carotid-cavernous fistula, both due to damage to the optic nerve at the time of the original injury (two cases in this series) and to injury as the result of venous dilatation. Papilledema may be present but usually the retina merely shares with the general dilatation and tortuosity of the orbital and conjunctival vessels. Blindness in the affected eye occurs in almost one-third of cases and some loss of vision in practically half of the cases.

Other cranial nerves may be affected, particularly in the first branch of the trigeminal, but as the result of the basal skull fracture any others, especially facial and olfactory nerves. In one case of this series severe pain in the forehead was present for a year before an ophthalmoplegia, and in another case a facial paralysis resulted from the original injury.

The symptomatology of carotid-cavernous aneurysms – unilateral or bilateral pulsating exophthalmos, a bruit audible to both patient and physician, and often involvement of the optic nerve or paresis of extraocular movements – is thus so

typical that its clinical recognition should cause no trouble.

Supraclinoid Aneurysms

Some 71 verified aneurysms of the internal carotid artery occurring above the clinoid process comprise the basis for this study. It is difficult to divide the symptoms into those occurring before and after rupture since the time of rupture is not always known.

Of the 46 patients having subarachnoid hemorrhage, 23 had no premonitory symptoms. Headache or head pain was the most common complaint and was present up to many years before rupture. Ten patients complained of headache of a more or less diffuse nature, three of suboccipital pain, and three of pain in the eye. A hemiplegia occurred in three instances many years before other evidence of an aneurysm and it might be questioned if the two were related. However, the aneurysm in each case was present in the hemisphere contralateral to the paralysis. In one patient diplopia was a premonitory symptom. One patient had a series of unconscious attacks before other manifestations, and one complained of dizzy attacks several years before other symptoms.

In this entire group, before or after rupture of the aneurysm, by far the most common earliest symptom was headache or pain in the head; this was specifically mentioned in 51 of the 71 cases. This symptom was present for as long as 14 years before a frank rupture occurred. In five of these cases the pain was referred to the occipital region and in eight cases to the eye or behind the eye. One of the latter patients stated that he had had his initial pain three years before a frank rupture with recurrence of the pain and progressive coma. In some cases the pain was referred to the temple. A typical migraine history with scintillating scotomata was not elicited in any case.

The next most common symptoms were failing vision and hemiplegia. Some impairment of vision was noted as the initial symptom in six cases. This was usually a scotoma but hemianopsia and unilateral blindness were noted. The visual disturbances were present for as long as two years before medical attention was sought. In one case unilateral blindness was present three months before a fatal rupture of the aneurysm occurred. Hemiplegia occurred as many as 40 years before other evidence of the aneurysm was present. In one case hemiplegia occurred with coma 20 years previously and in another four years before. The hemiparesis was usually associated with some degree of aphasia if the lesion was in the dominant hemisphere. In some cases it was very mild and almost completely cleared up.

In six cases the first manifestation of the aneurysm was coma without premonitory symptoms; in one case epigastric pain preceded shortly the onset of coma. In 18 other cases coma developed after other symptoms, usually severe headache. An ensuing coma was a poor prognostic sign, for only three patients in this category survived the acute stage.

Diplopia occurred as the first manifestation in four cases, but an accurate account of the images is not available. It was associated with other evidence of third nerve paralysis, usually ptosis.

Of the secondary (those following one of the previously mentioned complaints) symptoms, ptosis (23 cases) and diplopia (20 cases) seemed to be the most common. Vomiting was mentioned in 12 cases but probably occurred in other cases also. Pain in the head or headache

was a secondary symptom in 16 cases so that 67 of the 71 cases complained of some type of head pain. In this group six patients complained of stiffness of the neck. Hemiplegic manifestations occurred in five instances, blurred vision in three. Tinnitus and deafness were complained of each in one instance. Convulsions occurred in six patients.

Thus it is of interest that almost all patients, even those without rupture, complained of some head pain and that 14 patients localized the pain to the eye. Of note is the presence of hemiparesis of some degree in 11 patients and the presence of ptosis in 23 instances. A history of subarachnoid hemorrhage or the presence of blood in the spinal fluid was noted in 46 of the 71 cases. Of these patients 14 were found to have arterial hypertension; seven of the 23 patients not having subarachnoid hemorrhage had high blood pressure.

Other than the previously mentioned findings and those associated with the meningeal irritation of subarachnoid bleeding, a paralysis of the third cranial nerve on the side of the aneurysm was the most common finding, being present in 40 cases. In seven cases other nerves to the ocular muscles were involved, in five instances the fourth and in two the sixth (one an isolated sixth nerve palsy). In six instances the trigeminal nerve was said to be impaired. As mentioned previously, the optic nerve was injured in five instances and perhaps a sixth instance. A hemianopsia was present in two cases.

It is evident that there is no pathognomonic picture of supraclinoid aneurysms either before or after their rupture. Only by considering the group as a whole can a differential anatomic diagnosis be suggested, and then only statistically.

The syndrome produced by aneurysms of the intracranial portion of the carotid artery has received more attention than any of the other symptom complexes produced by intracranial aneurysms. Sosman and Vogt[7] in 1926 formulated the syndrome produced by these unruptured aneurysms. Three years later Albright[8] divided the signs and symptoms into two main headings: 1) the neighborhood signs, and 2) signs and symptoms due to leakage from the aneurysm. He noted that the commonest neighborhood symptom was paralysis of the third nerve and involvement of the first branch of the trigeminal nerve. McKinney and co-workers[9] in 1936 emphasized the changes visible in the roentgenograms due to aneurysms of the intracranial portion of the internal carotid artery. They concluded that the classic syndrome of an unruptured aneurysm of the intracranial portion of the internal carotid artery consisted of exophthalmos and a partial or complete involvement of the second, third, fourth, fifth, and sixth cranial nerves on the side of the aneurysm. The third and fifth nerves were always involved and the others usually involved. Exophthalmos was probably unduly emphasized since they did not differentiate the syndromes produced by infra- and supraclinoid aneurysms. That the symptomatology was not pathognomonic they admitted, but they thought that the syndrome should raise the suspicion and roentgenographic evidence of bony destruction of the sella turcica, including the anterior clinoid processes, with or without linear streaks of calcification which are so frequently seen in this type of aneurysm, confirm the existence of the condition.

Parker[10] described the syndrome of aneurysms of the internal carotid and

middle cerebral arteries, depending on compression or leakage, as pain in the ophthalmic distribution, paralysis of the third, fourth, and sixth cranial nerves, exophthalmos, occasionally papilledema, and rarely erosion of the sella with dyspituitarism, optic atrophy, and hemianopsia.

Geoffrey Jefferson[11] pointed out that aneurysms which impinge upon the visual apparatus may spring not only from the internal carotid artery but from the posterior communicating artery, the anterior cerebral artery, the anterior communicating artery, or posterior cerebral artery.

ANEURYSMS OF THE ANTERIOR CEREBRAL ARTERIES OR ANTERIOR COMMUNICATING ARTERY

This series consists of 37 aneurysms of the proximal part of the anterior cerebral artery verified by angiography, autopsy, or operation. Of this group six were incidental findings at autopsy and apparently asymptomatic. The remainder were responsible for clinical symptoms.

Other vascular anomalies were present in four of these cases – in two, other intracranial aneurysms, and in two, coarctation of the aorta.

Symptoms may be present for several years before rupture or merely a few minutes. Eleven of the patients (35 per cent) had no premonitory symptoms before the rupture rendered them comatose.

The most common premonitory symptom (15 cases) was headache, which may have been experienced for two or more years before rupture. The headache was not characteristic, most patients complaining of a nondescript headache. Perhaps if the patient were seen before the rupture a better description of the pain might be obtained. Five patients complained of head pains rather than headache and two patients referred it behind the involved eye. One patient referred the headaches to the frontal region and one to the neck.

A decrease in vision was a premonitory symptom or the only manifestation (three cases) of the aneurysm in four cases. The visual loss varied from a small scotoma to a complete blindness. Photophobia was associated with the visual impairment in one case.

Epileptic manifestations initiated the symptomatology in two cases; in one instance the attacks consisted of twitching confined to the arm and hand, and in the other unconscious spells occurred.

The diagnosis was made at the time of rupture of the aneurysm in 27 of the 31 cases. Arterial hypertension was present in 18 of these cases, but did not occur in any cases which did not rupture. In three cases the diagnosis was established at operation for impaired vision, and in one patient who suffered headaches for years angiography disclosed the lesion.

As might be expected after rupture, the majority of the patients were in coma (20 of the 31) and those conscious were suffering from headache. One patient had a third nerve paralysis on the side of the rupture which may have been due to a hematoma about the small aneurysm. Eleven patients had convulsive seizures; in three cases these were focal and in the remainder general. Convulsions occurred in three patients not comatose and two of these survived. Three patients had a demonstrable hemiparesis, one of which was due to an intracerebral clot. In three moribund patients a quadriplegia was present with evidence of decerebrate rigidity.

Again, a typical clinical picture is not evident in the aneurysms of the anterior cerebral or communicating arteries, but a comatose patient with a history of visual impairment and no oculomotor palsy would appear likely to be suffering from an aneurysm of the anterior carotid artery. The varied symptomatology of aneurysms of the anterior cerebral and communicating arteries has been previously noted by Dandy[12] in a review of the literature to 1944.

Parker[10] concluded that aneurysms of the anterior cerebral or the anterior communicating artery without rupture or with only mild leakage may produce symptoms similar to those described in connection with aneurysm of the middle cerebral or internal carotid, except that bitemporal or homonymous hemianopsia and loss of smell are more likely to be present.

In his detailed discussion of the syndrome of the anterior cerebral artery, Critchley[13] appends a short discussion on aneurysm of the anterior cerebral artery and its branches. In the great majority of cases there have been no focal or general signs of localizing value. Among the focal signs he considered affections of the first and second cranial nerves on one side important, but concluded that "it is rarely possible to predict from the clinical signs that the aneurysm lies on the anterior cerebral artery."

Not sufficient cases are present in this series to warrant a discussion of the findings in aneurysms of the distal parts of the anterior cerebral artery.

ANEURYSMS OF THE FIRST PART OF THE MIDDLE CEREBRAL ARTERY

Some 28 verified aneurysms were located in the proximal part of the middle cerebral artery; only five of these did not rupture before the diagnosis was made (two were asymptomatic). In the latter group the symptomatology was quite varied – in two cases hemiparesis, and in one case each, headache, numbness of the face, and diplopia and ptosis. In the group which ruptured, prerupture symptoms were not common, only nine of the 23 patients having some degree of headache. Hypertensive vascular disease was common to both groups, occurring in two of the five unruptured patients and in 12 of the 21 patients whose aneurysm ruptured.

Hemiplegia was common in the ruptured cases, 13 of the patients having some degree of weakness after the rupture. Thirteen patients developed coma, preceded by headache or confusion. Other varied symptoms occurred: headache (three patients), convulsions (two patients), vomiting (one patient), and pain in the neck (one patient).

In the entire group convulsions occurred at some time in six cases. Some degree of hemiparesis was present in 15 cases. Coma occurred in 19 cases and was a poor prognostic omen, since all but one patient died. In these cases at least six were shown to have intracerebral hematomas. Of the entire group of 28 cases only one had a third nerve paralysis, probably due to a hematoma associated with the aneurysm. Several patients had associated abnormalities, one a coarctation of the aorta, one a cerebellar hemorrhage, and two a rheumatic endocarditis.

No classical picture of aneurysm of the first part of the middle cerebral artery has developed; however, a hemiparesis in the absence of cranial nerve involvement would make such an aneurysm suspect. This conclusion confirms the re-

ports of other authors. Schmidt,[14] Krayenbühl,[15] and German[16] all agreed that an aneurysm of the middle cerebral could not be diagnosed before rupture. After rupture, as Frankel and Alpers[17] emphasized in their recent review of the subject, the picture of a sudden loss of consciousness with previous headaches and occasional seizures associated with hemiparesis and signs of subarachnoid hemorrhage are very suggestive of an aneurysm of the middle cerebral artery.

ANEURYSMS OF THE POSTERIOR CEREBRAL AND POSTERIOR COMMUNICATING ARTERIES

It is difficult to be sure of the origin of certain aneurysms arising from the region of the posterior communicating artery. Those arising from the bifurcation of the internal carotid are included in the supraclinoid aneurysms and those arising from the junction of the posterior communicating and posterior cerebral in the latter group. There remain some ten aneurysms which seem to be related entirely to the posterior communicating artery. This series is rather small. In seven of the cases subarachnoid hemorrhage occurred. In this group headache or head pain was present for a variable period of time before definite evidence of rupture in all but one case in which a sudden coma occurred. Hemiparesis was present in three of these cases at the time of examination but only one patient was in coma and only one patient had hypertensive vascular disease. A third nerve paralysis was present in three cases and a fourth nerve in one. In the three cases without subarachnoid hemorrhage, a third nerve paralysis was present in two and a fifth and sixth cranial nerve weakness in the third.

Only five cases of aneurysm of the posterior cerebral artery are included in this series. All ruptured and three patients were in stupor or coma. The series is too small to draw further conclusions regarding the syndrome.

Obviously no typical clinical picture can be developed from the evidence presented here of the aneurysms of the posterior communicating artery.

BASILAR AND VERTEBRAL ANEURYSMS

Aneurysms of the basilar and vertebral arteries are difficult to diagnose during life. In this series of 17, five were asymptomatic and found only at autopsy, and seven produced no localizing signs until their rupture. In the remainder, hemiparesis was present in two cases, and cranial nerve involvement from III to VIII in the others. Dizziness on turning the head to the left with cerebellar signs was present in another. There was no distinction between the symptomatology of aneurysms of the basilar and vertebral arteries.

Dandy[12] calls attention to the "S-shaped elongations" of the basilar artery which occur in the elderly and are associated with atherosclerotic disease. These vessels, elongated and usually bulging to the left, tend to impinge upon the fifth or eighth cranial nerve giving symptoms of tic douloureux or Mènière's syndrome.

Parker[10] believed that these aneurysms of the posterior cranial fossa tended to reach a relatively large size before they ruptured, so that intermittent signs of pressure on contiguous structures are frequent. The course is intermittent and various evidences of involvement of the lower brainstem may be present, such as vertigo, hemianesthesia, hemiparesis or paraparesis, dysphasia, dysarthria, tinnitus, paralysis of one side of the tongue, and respiratory disturbances.

B. VASCULAR ANOMALIES

The cerebral vascular tumors may be divided into two main groups – 1) the vascular neoplasms (i. e. hemangioblastoma), and 2) the vascular malformations (i. e. angiomas, telangiectases, and so on) which at times may have the appearance of a tumor. This study concerns only the latter type of vascular abnormality and is based upon a series of 84 cases verified by angiography in nine, operation in 76, and autopsy in 17 (five "silent").

SUPRATENTORIAL LESIONS

The clinical symptomatology begins some time after infancy. None of the cases in this series had any neurologic disturbances dating from birth. The condition may exist throughout life without giving rise to any symptoms, being found as an accidental finding at autopsy. Such was the case in two patients of this series. But 90 per cent of patients have symptoms before the age of 40 years. The duration of symptoms ranged from one day to 25 years, averaging six years, but approximately 80 per cent of the patients had a history of symptoms for more than two years.

The most common symptom is epilepsy (table 1), which was the presenting complaint of 40 of the 64 patients with supratentorial lesions. In 26 cases the seizure was a localized Jacksonian seizure, in eight cases the attack had focal manifestations but became generalized, and in six cases the generalized attacks had no focal component. The localized attacks were usually associated with lesions of the central region of the cortex. The focal manifestation corresponded as might be expected to the appropriate cortical area (table 2).

The next common symptom was a neurologic deficit – in 13 cases a hemiparesis. The hemiparesis was usually of the spastic variety and associated with an intracerebral hematoma in five of the 13 cases.

Manifestations of subarachnoid hemorrhage were the presenting complaint in 14 cases. In five instances the patient was comatose at the time of admission. The bleeding occurred without warning and did not seem to be associated with arterial hypertension. In seven cases the subarachnoid bleeding was associated with arterial hypertension.

Intracranial hypertension was present in two cases. One patient had a medial

TABLE 1
INCIDENCE OF CERTAIN PHENOMENA IN CEREBRAL VASCULAR ANOMALIES

Symptom or Syndrome	*Number of Cases*	
	Supratentorial	*Subtentorial*
Convulsive seizures	40	0
Hemiparesis		
Subarachnoid hemorrhage	14	2
Intracranial hypertension	2	11
Visual disturbance	6	3
Intracranial noise	8	1
Headaches	4	2
Cranial nerve palsy	2	2
Mental disturbance	2	0
Exophthalmos	1	0

TABLE 2
INCIDENCE AND LOCATION OF LESION IN CHRONIC EPILEPSY

Location	*No. Cases*	*No. Epilepsy*	
		Focal	*Generalized*
Central	33	26	3
Sylvian	6	3	–
Temporal	8	2	–
Frontal	10	3	2
Occipital	6	–	1
Parietal	1	–	0
	64	40*	

*In two cases not included in these figures, generalized convulsions occurred after a subarachnoid hemorrhage shortly before death.

frontal anomaly with several subarachnoid hemorrhages in a period of three months, which might have been a factor. The hypertension of the second patient was minimal and manifested only by papilledema in the right eye. He had only an exploration and was alive and unchanged 16 years later so that his symptoms had not progressed.

Cranial nerve palsies were associated with intracranial hypertension and, in each instance, a sixth nerve paralysis. Visual disturbances were of the nature of a partial loss of vision usually associated with a hemianoptic defect due to a temporal or occipital vascular malformation. Noises in the head were noted by eight patients. Usually the noise was a roaring or pulsating sound. In five of these cases a bruit could be heard on auscultation.

Headache was present no more frequently than would be expected in the general population. It did not have any typical pattern.

The question of the progressive nature and symptomatology of these vascular malformations has not been answered conclusively. Holman[18] and Olivecrona and Riives[19] remark categorically of the "undoubtedly progressive nature" of the lesion. Cushing and Bailey[20] assume that "the lesions have as their basis a congenital malformation of the blood vessels which at a later period in life takes on increased activity from some sort of stimulus," but one may wonder how seriously they take this when later they state that "the activation of the lesion has been ascribed to puberty . . . to excessive worship of Venus, Bacchus or Vulcan." The predisposing cause of the onset of symptoms in adult life might be related to cerebral softening resulting from the pulsations of the tumor, from

TABLE 3

INCIDENCE OF SIGNS AND SYMPTOMS IN THE VARIOUSLY LOCATED ANEURYSMS AND VASCULAR ANOMALIES

	Before Rupture				*After Rupture in Subarachnoid Space*										
					Involvement of Cranial Nerves										
	Asymptomatic	*Headache*	*Paresis III Cranial Nerve*	*Chance of Rupture*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*	*Coma*	*Hemiparesis*	*Convulsions*
Supratentorial vascular anomalies	+*	+	0	+	0	0	0	0	0	0	0	++	++	+
Aneurysm of internal carotid artery														
Infraclinoid	0	0	+++	+	+	+++	+++	+	+++	0	0	+	0	0
Carotid cavernous fistula	0	+	+†	0										
Supraclinoid	++	++	++	+++	+	++	+	0	0	0	0	+	+	+
Aneurysm of anterior cerebral and communicating arteries	++	++	0	+++	+	0	0	0	0	0	0	+++	+	+
Aneurysm of middle cerebral artery	+	+	0	+++	0	0	0	0	0	0	0	++	++	+
Aneurysm of posterior communicating and cerebral arteries	+	++	+	+++	0	++	+	+	+	0	0	+	+	+
Aneurysm of vertebral and basilar arteries	++	+	0	+++	0	0	0	0	0	+	+	+++	+	0

*Convulsions common.
†Syndrome of pulsating exophthalmos, bruit and at times ocular palsies.

Rating:
0 = 0–5%
+ = 5.1–35%
++ = 35.1–65%
+++ = 65.1–95%
++++ = 95.1–100%

changes due to thrombosis or hemorrhage of the vessels, or to degenerative changes in the abnormal channels. Certainly a case could be made out for each of these from the pathologic findings. Such an explanation of the onset of symptoms would not require the assumption of progressive enlargement of the lesion, for which we have, as far as can be ascertained, no proof. As a matter of fact, progressive degenerative changes (calcification) have been demonstrated in some cases followed by serial roentgenograms of the skull. The fact that 12 of these patients with confirmed cerebral vascular anomalies have been followed more than ten years, and some for as long as 26 years, with no change in their condition would argue against significant progression of the lesion.

SUBTENTORIAL LESIONS

The clinical findings associated with subtentorial vascular anomalies, summarized in table 2, are not characteristic and with rare exceptions are those accompanying any space-occupying lesion in the posterior fossa. Only the chance occurrence of subarachnoid hemorrhage, intracranial hypertension, and cerebellar signs would suggest the proper diagnosis.

DISCUSSION

While it is difficult to establish definite syndromes for aneurysms of the various intracranial arteries, there is sufficient difference in their biologic characteristics to suggest the location and type of lesion in many cases. The accompanynig table 3 indicates the points of differential diagnosis.

Usually the clinician has at his disposal other aids to diagnosis – electroencephalograms and skull roentgenograms, both of which may be of value. The roentgenograms of the skull are particularly useful since they may reveal calcifications in the wall of the aneurysmal tumor or local body erosions.

Finally with these findings the clinician can usually determine the side of the lesion and make an angiogram for accurate pathologic diagnosis.

SUMMARY

On the basis of an analysis of 285 aneurysmal tumors, the syndromes associated with aneurysms of the major intracranial arteries are discussed.

Although pathognomonic syndromes are not present, the symptoms associated with aneurysms of the internal carotid artery, either below or above the clinoid process, are often sufficiently characteristic to suggest the diagnosis. Aneurysms of the anterior cerebral and communicating arteries often produce visual disturbances and with rupture, sudden coma. Aneurysms of the middle cerebral artery are commonly associated with hemiparesis. The dilatations of the basilar and vertebral arteries may cause cranial nerve irritation or brainstem involvement.

Hemorrhage occurs from a vascular anomaly or angioma in 20 per cent of such cases. The nature of the lesion may be suspected by a long history of previous epileptic phenomena.

A table indicating the points of differentiation of these lesions is presented.

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■ The question I am about treating has had a singular fate; considered as solved for a great many centuries, it has hardly been the object of the attention of scientific men in our days. Until 1849, when I first published the discovery I had just made, that there is a decussation of the conductors of sensitive impressions in the spinal cord, it had been universally admitted that Galen had proved that there is no such crossing in the spinal cord, and that, therefore, these conductors must make their decussation in the encephalon. Physiologists and pathologists agreed in attributing to Galen the merit of having given a demonstration, in this respect, although he seems never to have tried to solve the question. In detailing his experiments on the spinal cord, he does not say a single word concerning sensibility, and it is upon the falsely understod results of these experiments, that for a great many centuries, medical men have based their opinions that there is no decussation of the conductors of sensitive impressions in the spinal cord.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Myofascial Pain Syndromes

Anders E. Sola, M.D. and Robert L. Williams, M.D.***

ALTHOUGH PAIN is the commonest complaint encountered by the physician, it is still poorly understood and often very refractory to treatment. In our experience in a large hospital, myofascitis as a clinical entity represents one of the most frequent causes of pain in a military population. This entity has not received the attention it deserves until recently. This may be so because of the wide variety of clinical symptoms presented, the diffuse and variable nature of the pain patterns, or the unpredictable response to treatment.

To date, much of the work with this entity has been done in the field of physical medicine. Travell,[1] Good,[2] and others have done much to demonstrate the high incidence of its occurrence as a clinical entity and have outlined an effective regimen for its treatment. It was felt that there was a need for a combined study by investigators in neurology and physical medicine, and this report is the result of such an approach. The need to explore new therapeutic methods is particularly important for neurologists.

The term "myofascitis" is used in preference to terms such as muscular rheumatism, fibrositis, myositis, fascitis, and myalgia, although they are often used to describe essentially the same entity. The myofascitic syndrome may present a wide variety of clinical symptoms. These include pain, stiffness, limitation of motion, tremors, weakness, and manifestations of autonomic nervous system dysfunction. However, the chief complaint of the patient is usually pain, which may vary in quality and intensity from a low grade discomfort to a type of pain that is severe and incapacitating and frequently associated with a deep, burning, aching sensation.

Many workers have demonstrated the presence in such cases of small abnormally sensitive areas of tenderness in muscle or other connective tissue. Upon pressure or other local stimulation these sensitive points appear to trigger the myofascial pain syndrome. The pain pattern arising from stimulation of a trigger point may be local in distribution, or it may radiate or be referred to a site at some considerable distance from the point of stimulation.

The commonest predisposing factor appears to be acute or chronic mechanical stress; however, precipitating factors

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FIG. 1. The attachments of the levator scapulae muscle are shown and the common location of the trigger point is indicated by the cross. The hatched area represents the common distribution of pain in this syndrome.

can be any type of stress, either psychogenic or organic.

It has been hypothesized that stimulation of the trigger point results in noxious impulses which bombard the central nervous system. If the stimulation exceeds the threshold, a reflex cycle is set up whereby the sensation of pain may be referred to another area. These reference sites do not follow the well known peripheral sensory nerve patterns, and this has led to delay in their acceptance as objective findings. In the past many persons have been inclined to brush aside consideration of these syndromes by calling them functional. However, one cannot discount the repetitious and constant nature of the patterns of pain referral. The trigger points are found repeatedly in the same place in the involved muscles and cause pain distributions in the same area in hundreds of patients. One would not expect such a constant pattern if the syndromes were entirely functional in origin. In addition, in recent months the authors have made two other observations which militate in favor of the presence of a physiologic disturbance. Stimulation with negative galvanic current in the area of the trigger point produces discrete areas of erythema over the trigger point. Exploration with a neurodermanometer, which measures skin resistance when altered by sweating, reveals a dramatic deflection of the needle as the trigger point is crossed. The deflection is invariably indicative of an area of decreased skin resistance. These two observations suggest that there is an alteration of vaso-

FIG. 2. The attachments of the infraspinatus muscle are shown and the common location of the trigger point is indicated by the cross.

motor activity in the area of the trigger point, which is rather sharply localized and irritable.

The trigger points can occur in any muscle; however, in the upper trunk they commonly occur at points in the levator scapulæ, infraspinatus, trapezius, and pectoralis major muscles.

In the lower trunk the common trigger points are found in the region of the quadratus lumborum, gluteus medius, tensor fascia lata, gastrocnemius, and anterior tibialis muscles. Several of the more common trigger points and the pain syndromes they produce will be discussed.

LEVATOR SCAPULÆ SYNDROME

Patients who complain of pain and stiffness at the base of the neck on one side, involving the posterior medial aspect of the shoulder, are frequently found to have trigger points in the levator scapulæ muscle at or near its attachment to the scapulæ. These trigger points may be located by deep palpation in the area which will elicit the tender point and reproduce the radiation of pain. They also may be located by electrical stimulation. The pain radiates into the neck and back of the head. The flareup of trigger points in the levator scapulæ as a result of one form of stress or another is one of the commonest causes of torticollis in our experience. It should be noted that the levator scapulæ is placed under stretch in rotation of the head or the scapulæ. The side of the trigger point cannot always be predicted by noting the side to which the head tilts but must be determined by palpation. Figure 1 shows the attachment of the levator scapulæ, the trigger point, and the area of pain reference.

FIG. 3. The attachments and landmarks around the quadratus lumborum are shown. The crosses indicate common locations of trigger points in this syndrome. The hatched area represents the usual area of pain.

INFRASPINATUS MUSCLE SYNDROME

A common cause of shoulder pain in young adults is found to be secondary to trigger points located in the inferior lateral portion of the infraspinatus muscle. Pain associated with these trigger points is usually referred to the anterior lateral aspect of the shoulder and frequently may radiate into the hand, simulating dermatonal patterns of the brachial plexus. Associated symptoms include shoulder girdle fatigue, weakness of grip, loss of range of motion of the shoulder, hyperhidrosis, and skin temperature changes. The location of the muscle, its attachments, and the com-

FIG. 4. The attachments of the tensor fascia lata and the gluteus medius are shown. The crosses indicate the common locations of trigger points.

mon location of the trigger point are shown in figure 2.

QUADRATUS LUMBORUM SYNDROME

Unilateral low back pain in young adults is commonly found to be secondary to activation of hypersensitive areas in the quadratus lumborum muscle. These trigger points are commonly found over the transverse processes of the first three lumbar vertebra or at the insertion of the quadratus lumborum on the twelfth rib. Trigger points in the quadratus lumborum muscle may produce local pain in the area shown in figure 3. It is also a frequent cause of anterior abdominal pain and pain in the anterior aspect of the thigh. The landmarks shown in figure 3 are the crest of the ilium, the dorsal spinus processes of the lumbar vertebrae, the twelfth rib, the borders of the quadratus lumborum muscle extending from the crest of the ilium to the twelfth rib, and the common locations of the trigger points.

TENSOR FASCIA LATA SYNDROME

Trigger points in the tensor fascia lata, in our experience, are frequent causes of pain in the hip and anterolateral aspect of the thigh. It is suggested that the syndrome of meralgia paresthetica may be secondary to the trigger points in the tensor fascia lata. Figure 4 illustrates the occurrence of trigger points in the tensor fascia lata and gluteus medius. Hypersensitive areas in the gluteus medius have been found to be frequent causes of pain in the hip, thigh, and calf.

ANTERIOR TIBIALIS

Pain in the anterior lower portion of the leg, ankle, and foot is a common complaint in a military population, and in our experience has been frequently associated with painful trigger points in the dorsi flexors of the foot, particularly the anterior tibialis. Figure 5 demonstrates the location of the anterior tibialis muscle and the usual location of the painful trigger point.

TREATMENT

Treatment is aimed at elimination or desensitization of the hypersensitive trigger points. For many years injection of analgesics and various other substances into the tender points has been used with considerable success. We originally injected these trigger points, using dilute analgesics such as procaine, pontocaine, and so on. However, use of local analgesics is not without its dangers. Many individuals have a mild hypersensitivity

to local analgesics which causes lightheadedness, palpitation, and mild hypotensive reactions. In order to avoid the possibility of these side effects, the authors have introduced the use of isotonic sodium chloride and physiologic saline for injection of the trigger points. This injection technic has been used in over 1,000 cases at Lackland Air Force Base Hospital. This procedure has both therapeutic and diagnostic value. If no relief is obtained from a series of several injections, further diagnostic procedures are indicated to rule out the presence of another lesion.

In our experience, saline was found to be as effective as local analgesics for therapy. A favorable response to saline injections has been judged in the past as evidence of psychogenic etiology. The element of suggestion cannot be denied, but it seems obvious in this series that something more than suggestion was in effect. One possible explanation is that the solution exerts pressure on the site of the trigger point and adjacent pressor receptors, which in turn effect an alteration of the vasomotor activity in the area. In the course of this study, an abundance of clinical evidence demonstrating the presence of alterations of autonomic nervous system activity was found. These disturbances included local or segmental variations in skin temperatures and sweat patterns, reflex loss of joint range, tremors, and edema. Many of the syndromes simulated the early manifestation of reflex dystrophies. These disturbances were decreased or disappeared entirely following the saline injections.

The histopathology of these trigger points has been investigated but to date the findings are meager and are not too helpful in explaining the pain.

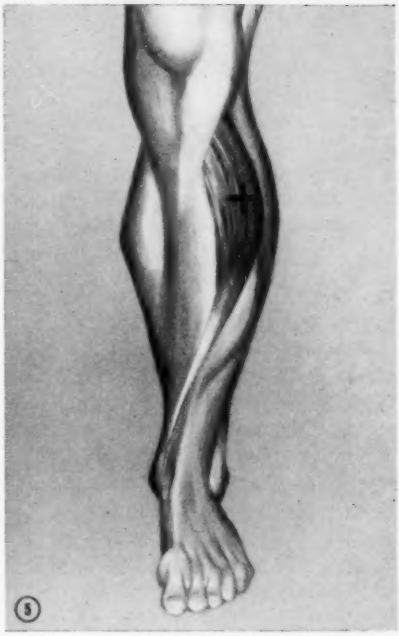

FIG. 5. The attachments of the anterior tibialis and the common location of the trigger point are shown.

CONCLUSION

In summary, we would like to suggest that in our experience myofascial pain syndromes are so common that they should not be overlooked when one is faced with a pain problem which does not fit familiar clinical patterns. In patients in whom hypersensitive trigger points are found, the use of saline injections into the area both for diagnostic and therapeutic purposes is recommended.

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Craniovascular Studies in Headache

A Report and Analysis of Pulse Volume Tracings

Percy Brazil, M.D. and Arnold P. Friedman, M.D.

THE RELATIONSHIP between cranial arterial circulation and headache has long been established.[1] In the past few years several papers have been published establishing a method of direct measurement of the volume changes occurring in various branches of the external carotid circulation.[2–4] We have utilized these principles in our studies, and in addition have added a further method of photoelectrometric measurement of the volume changes occurring in the branches or tissue areas supplied by the external maxillary artery.

The subjects on whom the studies have been performed have been patients with migraine, tension headache, or muscle contraction headache, and normal individuals who are not troubled with headache. The patients with migraine and tension headaches were studied in both the headache and headache-free phases. In order to differentiate between the two types, it is best to define clearly our criteria for the diagnosis of both migraine and tension headaches.

MIGRAINE

Clinical picture. Migraine may be defined as that form of headache which is characteristically paroxysmal, periodic, unilateral, and throbbing.[5] The headache occurs against a background of relative well-being, is often preceded by visual or psychologic disturbances, and is usually associated with irritability.

Physiologic mechanisms. The following physiologic changes occur in an attack of migraine:[6] An initial vasoconstriction of certain intracranial branches of the internal carotid artery produces visual and possibly other preheadache phenomena prior to the onset of headache. This prodromal period is followed by dilatation and distention of cranial arteries, primarily in the distribution of the external carotid artery. Stimulation of pain-sensitive nerves in and around the dilated vessels by the increased amplitude of pulsation is the presumed cause of the headache. Persistent dilatation results in a rigid, pipelike state of the vessels. The pain at this stage is a steady ache replacing the earlier throbbing pulsation type. During or following this, there is contraction of the neck muscles and "muscle contraction pain" develops. This spasm of the muscles is a reaction to the initial pain and may outlast it. The initial phase of the head-

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ache is due to stimulation of pain endings which lie in or near the walls of the intracranial arteries, whereas the latter "muscle pain" is probably the result of either direct stimulation of nerve endings or ischemia of the muscles. Although the immediate cause of pain in migraine is associated with dilation of cranial arteries, it is evident that dilatation of blood vessels alone is not sufficient to produce headache. Other dynamic or chemical factors as yet not clearly delineated must contribute.

TENSION HEADACHE *(Muscle Contraction Headache)*

Clinical picture. Tension headache occurs in relation to constant or periodic emotional conflict, of which the patients are usually partially aware. There are no prodromata; they are usually bilateral, occipital, or frontal, and may be accompanied by a variety of associated signs including anxiety and nausea. Frequency and duration are variable.

Physiologic mechanisms. In tension headaches, muscular or vascular mechanisms may act independently or concomitantly.[7] With muscle tension, sustained contraction of the skeletal muscles of the head and neck causes pain or dysesthesia in the neck and scalp. Associated with these muscular spasms may be ischemia, which could be a contributory or primary factor in the induction of pain. It has also been hypothecated that excessive concentration of potassium in muscle from ischemia or sustained contraction stimulates the chemoreceptors in the tissues. Another factor responsible for the head pain may be a central spread of the excitatory factor of noxious stimulation of the soft tissues of the neck. This spread of pain is carried by the upper cervical nerves and may produce painful sensations in the forehead and face.

Under stress, a discharge may occur in the autonomic nervous system with resultant changes in the cranial blood vessels. The end organs for pain surrounding these blood vessels are stimulated and create nerve impulses which pass along the afferent pathways to the central nervous system.

METHODOLOGY

In our study of the extracranial circulation, two separate technics were employed:

1. Direct measurement of arterial pulsation was obtained by utilizing glycerine pellottes, which were placed over the arteries under study and held in position by a rubber band. The pellotte was connected in a closed circuit to a transducer, which in turn was connected with an amplifying system and a multichannel direct writing recorder. Pulsations of the artery were transmitted through the circuit, transformed into electrical signals, and traced on heat-sensitive paper as curves.

2. Through the use of photoelectrometric principles, we were also able to record qualitatively certain aspects of the blood flow in the areas of the face supplied by the external maxillary artery. A light was passed through a lucite rod, which was placed inside the mouth so as to distend both cheeks. Photoelectric cells were placed close to the external surfaces of the skin of the cheeks. As the area was suffused with blood during systole, the amount of light passing through the cheeks was diminished. This was recorded by the photoelectric cell and transmitted to a recorder, elevating the stylus of this recorder. More light was transmitted with

diastole and the diminution of arterial blood in the tissues, which depressed the stylus. Thus, using a continuous tracing, it was possible to record as curves the blood flow related to the branches or the tissues supplied by the branches of the external maxillary artery.

The pellotte was used for recording the volume changes in the temporal, occipital, and supraorbital arteries. The photoelectrometric technic was used only for the area supplied by the external maxillary artery.

Figure 1 represents the volume pulse curve of the right temporal artery in a patient free of headaches.

The pulse waves were studied with regard to certain characteristics: 1) rate, 2) regularity in rhythm and in appearance, and 3) amplitude. Blood pressure readings were taken regularly during the recordings. The tracings were obtained with patients in both the upright and recumbent postures.

From the onset it was obvious that there was no volume pulse curve which was typical of any of the three groups of patients under study. Indeed, a patient suffering with migraine (in both the headache and headache-free phases) could show a pulse wave which was similar in all the three above-mentioned characteristics to a pulse wave in a "normal," or to the pulse wave in a patient suffering with an acute tension headache (figure 2).

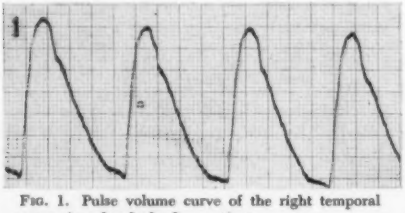


FIG. 1. Pulse volume curve of the right temporal artery in a headache-free patient.

In addition, within each clearly defined clinical group there were wide differences in the appearance of the pulse waves (figure 3). Thus it is not possible on the basis of an isolated series of pulse waves to determine which type of headache a given patient has, and further it is not even possible to gain an impression from isolated pulse waves as to whether a patient has a headache or not at the time the tracing is taken.

Other observers, using a similar pellotte technic, have indicated that the bilateral symmetry of arterial pulsations is disturbed in specific ways in certain types of headache and that the amplitude of pulsation varies accordingly. While this may be true, it seems to us that many considerable sources of error are present using this technic, and these have to be recognized or interpretations will be made which are not wholly valid. In the first place, the exact positioning of the pellotte over the artery determines to a large extent the size of the systolic limb of the pulse wave. Also the pressure applied in holding the pellotte against the artery determines the amplitude of pulsation which is recorded on the tracer. The greater the pressure the greater the amplitude (amplification remaining constant). When taking simultaneous bilateral tracings, it is extremely difficult to be sure that both pellottes are in exactly the same position with respect to the artery. It is also extremely difficult to be certain that the same amount of pressure is being utilized to hold each pellotte against its artery. Thus it is necessary to resist the temptation to compare the amplitude of pulsation of an artery on one side of the head with one on the other side, or tracings from one individual to those from another. From this it is obvious that even

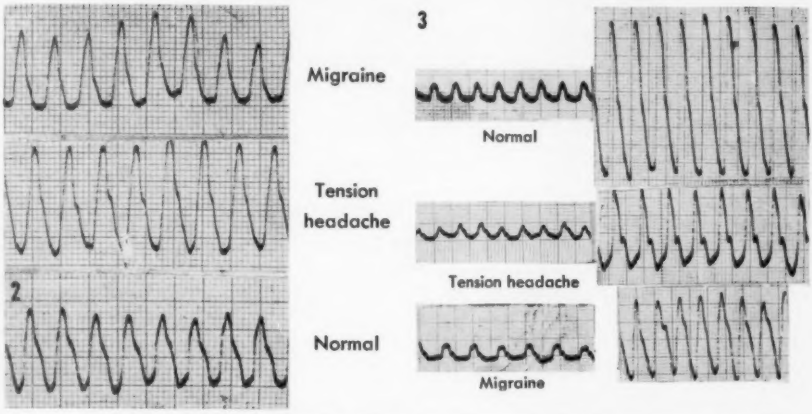


FIG. 2. Similarity of pulse volume tracings obtained in patients with migraine and muscle contraction headaches, compared to headache-free patient. FIG. 3. The variation possible in pulse tracing in each group is similar.

tracings taken on the same individual on different occasions must be interpreted with caution.

The variable factors involved in the photoelectrometric method are: 1) variations in cheek thickness in different individuals, 2) variations in skin pigmentation in different individuals, and 3) variations in the amount of cheek distention depending on the size of the buccal cavity. These three variables make meaningless any attempt at comparison of the amplitude of the waves from one individual to another. It is also a mistake, in interpretation of the waves obtained by either technic, to relate the size of the wave with the resting state of the vessel.

Recognizing these sources of error, it is possible, however, to obtain a considerable amount of useful information from cranial pulse volume tracings. The significant factors which can be studied are those changes that occur in the pulse wave in a given individual using a continuous tracing which can be related to subjective manifestations, namely, change in the headache status.

Our procedure consisted of taking tracings and injecting one of three preparations parenterally while the tracing was in progress. The three preparations used were dihydroergotamine, nicotinic acid, and sterile water. Dihydroergotamine (DHE 45—Sandoz) is the methanesulfonate of hydrogenated ergotamine, 1 cc. of which contains 1 mg. of Dihydroergotamine. Normally, Dihydroergotamine induces vasoconstriction of the extracranial arteries, while nicotinic acid produces a vasodilating effect. Objective and subjective responses to the injections were observed and recorded.

RESULTS

Migraine (Table 1)

One hundred and eighty-eight patients with migraine were seen, of whom 107 had headache when the tracing was started and 81 were headache free. Of those who had headache, 76 were given 1 cc. of DHE intravenously, and of these

TABLE 1
ANALYSIS OF 188 PATIENTS WITH MIGRAINE

HEADACHE PRESENT
(107 patients)

Drug	*Number of Patients*	*Headache Diminished*	*Headache Increased*	*No Effect*
DHE	76	69	0	7
Nicotinic acid	21	4	12	5
H_2O	10	0	0	10

HEADACHE NOT PRESENT
(81 patients)

Drug	*Number of Patients*	*Headache Induced*	*Headache Not Induced*
DHE	23	0	23
Nicotinic acid	25	8	17
H_2O	33	0	33

69 (91 per cent) showed pulse wave changes of diminished amplitude and experienced diminution of the headache which had been present. Seven (9 per cent) showed no subjective or objective response to DHE.

Twenty-one patients with migraine were given 100 mg. of nicotinic acid intramuscularly while the headache was present. Of these, 12 (57 per cent) experienced increase in the pain and an increase in the amplitude of pulsation. There was no effect on five (24 per cent), and four patients (19 per cent) showed subjective improvement and diminished amplitude. Ten patients of the 107 were given sterile water. There were no pulse wave changes or change in the headache status in any of these.

Of the 81 headache-free patients, 23 were given DHE. No headache was induced in any of these, and the pulse wave changes were those of diminished amplitude. Twenty-five patients in this migraine group who had no headache at the onset of the tracing were given 100 mg. of nicotinic acid. This succeeded in inducing a headache in eight patients, and at the same time increased the amplitude of pulsation of the relevant vessels. There was little or no effect on the remaining 17. Finally, 33 of the 81 in whom no headache was present were given 1 cc. of sterile water intramuscularly and this produced no effect.

Tension (Muscle Contraction) Headache (Table 2)

One hundred and three patients with tension headache were seen. The headache was present in 57 of these, 42 of whom were given 100 mg. of nicotinic acid. This completely eliminated the headache in 19 (45 per cent), partially relieved the headache in 14 (33 per cent), and produced no change in the headache in nine (22 per cent). There was increased amplitude of pulsation in all these 42 patients. Ten patients were given 1 cc. of DHE intramuscularly. This had no effect in nine patients and increased the headache in one patient. Five patients were given sterile water intramuscularly without subjective or objective response.

Of the 46 patients who were headache free at the onset of the tracing, 15 were given DHE, which induced

TABLE 2

ANALYSIS OF 103 PATIENTS WITH TENSION HEADACHE (MUSCLE CONTRACTION)

HEADACHE PRESENT
(57 patients)

Drug	*Number of Patients*	*Headache Diminished*	*Headache Increased*	*No Effect*
DHE	10	0	1	9
Nicotinic acid	42	33	0	9
H_2O	5	0	0	5

HEADACHE NOT PRESENT
(46 patients)

Drug	*Number of Patients*	*Headache Induced*	*Headache Not Induced*
DHE	15	4	11
Nicotinic acid	18	0	18
H_2O	13	0	13

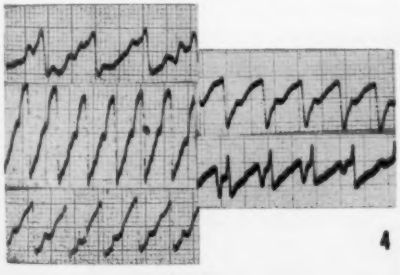
headache in four but did not induce a headache in 11. The pulse wave response was one of diminished amplitude. Eighteen of the 46 were given nicotinic acid which did not induce a headache in any, and 13 were given water which had no effect whatsoever.

DISCUSSION

Occasionally individuals were encountered in whom pulse wave patterns resembled mirror reflections of the standard patterns. In these the reversed pattern was constant (figure 4). No explanation is offered for this type of volume pulse wave. In other patients there was complete dissimilarity of the pulse wave contours, not only from each other on different sides of the head but also from the standard pattern (figure 5).

Another interesting variation was found in three patients. In this the volume pulse wave changed its amplitude with every successive heart beat (figure 6).

In addition to evaluating the qualitative vascular response of the cranial vessels to certain medications, we have recorded the time required for a vascular response. The drugs have been given



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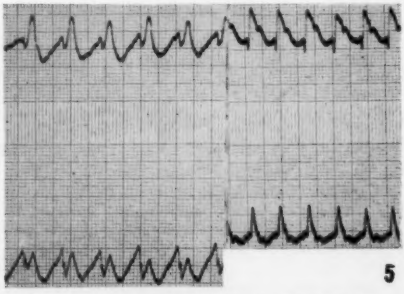

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FIG. 4. Pulse wave patterns resembling mirror reflections of standard pattern. FIG. 5. Complete dissimilarity of pulse wave contour bilaterally from the standard pattern.

FIG. 6. Successive changes in volume pulse amplitude with each systolic contraction.

by different routes of administration and in combination to study the effect of potentiation on the rapidity of vascular response.

In the course of these studies, it became apparent that the patient felt the effects of a medication before associated changes were seen objectively. For example, an intravenous injection of Dihydroergotamine would often produce a subjective response in less than two minutes, whereas no significant modification of the pulse volume tracing occurred for four to five minutes.

Perhaps even more interesting is the synergistic effect of caffeine and ergotamine tartrate on the cranial vessels. Caffeine given by itself does not produce any marked change in the volume pulse, while the effect of ergotamine tartrate is considerable. Yet the addition of caffeine expedites the time taken for both the objective and subjective responses to ergotamine tartrate to occur in comparison with its administration alone. Thus it would appear that caffeine potentiates the action of ergot on the cranial circulation.

SUMMARY

Based on these observations, the following conclusions relative to head pain are made:

1. The supposed mechanism of extracranial arterial volume changes occurring during a migraine attack is in keeping with our findings of the subjective or objective response to Dihydroergotamine, which succeeded in diminishing the volume pulse amplitude and easing the headache in a significant number of patients.

2. In patients with muscle contraction headache, a sufficiently significant number of patients evidenced such response to nicotinic acid as to postulate the belief that a local vascular insufficiency might play a definite part in the mechanism of pain. It may well be that such an insufficiency occurs secondarily to local muscle contraction.

3. The effects of drugs were felt by the patients before associated changes could be recorded objectively.

4. The field of pulse wave tracings and study is one in which understanding of the significance of the tracings is constantly growing. There are certain findings present in our recordings, the significance of which are not yet fully understood but which will be clarified by further experience.

Acknowledgment is made to Dr. Joseph M. White without whose able assistance certain phases of our investigation could not have been undertaken.
We wish to thank Dr. Adrian Kantrowitz for his advice and suggestions.

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Metastatic Lesions of the Vertebral Column Causing Cord Compression

Eben Alexander, Jr., M.D., Courtland H. Davis, Jr., M.D. and Charles H. Field, M.D.

SURGERY OF CANCER is fraught with disappointments and complications. Yet as the surgical field advances, types of cancer previously considered inoperable are being attacked and, in some instances, a measure of success obtained. Some surgeons have considered a 20 per cent survival rate, such as in the exenteration operation for pelvic carcinoma, a genuine advance justifying the effort and suffering involved.[1]

Metastatic lesions to the central nervous system occupy a peculiar position, since the metastases are solitary in some instances and in almost all cases the total mass of the lesion, when it produces symptoms and signs of pressure, is relatively small. There are several reports of metastatic brain tumors having been removed, with long term useful survivals. Cushing[2] reported one 65 year old individual with a solitary metastasis of a hypernephroma, who survived the removal of a brain metastasis for five years and ten months, working most of the time at his usual occupation.

The well known predilection of prostatic, thyroid, renal, and breast tumors to metastasize to bone has been emphasized many times.[3–9] It has been stated that approximately 20 per cent of carcinomatous metastases go to the spinal column.[10] Since routine complete removal of the spinal cord in autopsies is not commonly carried out, data on this aspect of the problem are not accurate. Damage to the spinal cord from metastatic lesions is produced by vertebral infiltration and fracture, by compression of blood vessels, by epidural compression of the cord, and rarely by infiltration of the spinal cord or cauda equina.[6,9,11] Many known destructive lesions of the spine do not produce any cord compression during the life of the patient and the patient succumbs from the general metastases. We are not concerned with this particular group of patients in this presentation.

RATIONALE FOR NEUROSURGICAL INTERVENTION

The concern of the neurosurgeon is with the patient who begins to develop signs of spinal cord compression. This may be with or without known cancer elsewhere in the body, and with or without any visible destructive lesion in the roentgenograms of the spine. The patient usually develops pain in the region of

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the involvement, often radicular, and in early stages commonly develops some difficulty in emptying the bladder and bowels. Subsequently, the intensification of radicular pain and the rapid progression of paresis to complete paraplegic below the site of the lesion is well known.

The objective of treatment in such cases is relief of cord compression before irreversible paralysis has occurred. The neurosurgeon is sometimes called to see the patient when neurologic signs are beginning, and decompressive procedures are commonly carried out as an emergency. The patient with metastatic cancer is happier and easier to care for if he is ambulatory than if he is paraplegic.

Roentgenograms of the spine and chest are helpful, as will be indicated below in a review of a series of cases, but in many cases no obvious lesion of the spine or chest will be evident. Lumbar puncture with a carefully performed Queckenstedt test is valuable. If there is any evidence of compression, Pantopaque myelography to determine the level of block is of the utmost importance. It is often necessary to invert the patient to a 90 degree angle to be certain of a complete block.

If life expectancy is more than a few weeks, early laminectomy and decompression is advisable. No effort is made to remove the tumor completely, but sufficient exposure should be obtained to decompress the cord completely throughout the involved area. On several occasions the dura has been opened and the dentate ligaments divided because of tumor anterior to the dura. It has not been our experience that this has contributed to the production of any generalized central nervous system metastases. Postoperatively local roentgen therapy may further relieve pain and benefit the patient; orchiectomy and estrogens in tumors of the prostate may also be beneficial.[12,13]

SURVEY OF MATERIAL

A series of 22 patients, 15 males and seven females, with metastatic lesions to the spine and its contents, with evidence of cord compression, has been reviewed. In this group 12 were totally paralyzed below the level of the lesion when first seen by the neurosurgical service. Seventeen of the 22 patients showed x-ray evidence of metastases to the vertebral column.

In 18 of the 22 patients, Pantopaque myelography was carried out. Fifteen of these showed a complete spinal fluid and myelographic block, and one had evidence of a partial block in the Queckenstedt test. With four exceptions, all of the patients operated upon had lesions in the thoracic spine from T3 through T11. Two of these exceptions had prostatic carcinomatous metastases. One showed an anterior dislocation of C1 on C2 with beginning cord compression, while the other had paraplegia from a metastasis to L2. The other two exceptions had metastases to the spinal cord or cauda equina. One was metastatic malignant melanoma at the T8 level, and the other was an adenocarcinoma metastatic to the cauda equina and conus medullaris. This case had roentgenographic findings suggestive of a primary lesion in the lung.

The average age of the patients was 51 years, ranging from 14 years in a patient with myelogenous leukemia to a 72 year old man with prostatic malignancy. The average duration of symptoms before coming to the neurosurgical

service was five months. Only eight of the 22 patients had initial evidence of primary malignancy elsewhere.

Surgery was performed on 21 of the 22 patients. The operation was decompressive laminectomy except for the patient with the C1 on C2 dislocation. In this case, a reduction of the dislocation and fusion was carried out, with orchiectomy and the administration of stilbestrol for prostatic malignancy. The one patient not operated upon was a 14 year old girl with myelogenous leukemia and local metastases to the lower cervical and upper thoracic spine in the extradural space. In this case, the reduction in platelets was so severe as to obviate the possibility of surgery and the expected length of life did not justify surgery.

The known origin of the metastatic lesions is listed below:

Prostate	6
Anaplastic carcinoma (primary site undetermined)	7
Malignant melanoma	1
Lung	1
Thyroid	1
Breast	1
Cervix	1
Plasmocytoma	1
Fibrosarcoma	1
Reticulum cell sarcoma	1
Myelogenous leukemia	1

RESULTS

In the 12 patients with complete paraplegia before surgery, there was no improvement following surgery except for the relief of pain. The average length of life after operation was approximately four months.

Of the ten patients who were not paraplegic before surgery, four are still living. One is alive three years after the removal of an extradural anaplastic tumor in the midthoracic region. He received intensive postoperative irradiation and is still doing well, working regularly, without evidence of recurrent tumor, and with only moderate neurologic deficit. The primary site of his tumor was not known at the time of surgery, nor is it known at present, as the microscopic sections revealed such an anaplastic tumor its origin could not be identified. The second patient has a prostatic metastasis to his upper thoracic spine. This patient's paraparesis was reversed by decompressive laminectomy and, although still living five months after surgery and not paraplegic, his downhill course is quite evident at this time. The third patient is alive five years after removal of a midthoracic anaplastic tumor and is without neurologic deficit. He received postoperative irradiation. The fourth patient had surgery only two months ago and is receiving roentgen therapy. There has been no progression of neurologic deficit.

The other six patients are all dead, having survived from four days to five years after surgery. Three died of postoperative complications. One patient lived for five years after decompression of the cord at T3 for a metastatic carcinoma from the thyroid. This patient lived a useful, relatively happy life following surgery, despite other metastases. Although he was partially paraplegic before the decompressive laminectomy, it can be reasonably stated that this patient obtained a good result. One patient lived five months after surgery and showed decrease in his paraparesis to the extent that he became ambulatory. Another patient who had malignant melanoma metastatic to the spinal cord lived three years after surgery, meanwhile suffering metastases to the left occipital lobe and later the cauda equina.

Certainly, therefore, if a patient is not already paraplegic prior to the time he is studied, a decompressive laminectomy will permit an occasional prolonged, useful survival, or at least an improved terminal problem.

For those patients already totally paraplegic, little seems to have been gained by decompressive laminectomy except for some relief of local pain. This same relief might well have been obtained by local roentgen therapy. However, in most of these cases the type of tumor was not known prior to surgery and, from the point of view of prognosis, the identification of a metastatic tumor was of help in predicting the eventual outcome for the patient. If the tumor is slowly growing and the paraplegia comes on over a period of several weeks, laminectomy might restore some motor function.

ADDITIONAL DATA

Attention should be called, through two illustrative cases, to the fact that the roentgenographic appearance of a destructive lesion may not be unequivocally diagnostic for metastatic malignancy. Operative intervention in such cases may at times be attended by excellent results, or occasionally, as in the first case below, may result in increased neurologic deficit.

Case 1.—A 68 year old woman who had had previous coronary disease was seen in March 1952, with severe pain in her low back and bladder difficulty. A gibbus was present at T11–T12 and there was some evidence of sensory loss below this. A roentgenogram showed a destructive lesion in the eleventh dorsal vertebra, and a myelogram showed a partial block at that level. Laminectomy disclosed a lesion in the body of the eleventh dorsal vertebra which was subsequently diagnosed pathologically as "fibrous dysplasia."

Postoperatively the patient developed a small extradural clot which was evacuated within five hours after the original procedure. In spite of this, she maintained a complete paraplegia below that level and has continued to live unhappily and in pain since that time.

Case 2.—A 58 year old woman with rheumatic heart disease was seen in August 1950, because of pain in the midthoracic region, radiation around to the chest and in the back, with beginning evidence of paraplegia. She showed hyperactivity of the tendon reflexes in the right lower extremity and a positive Babinski on the right. Roentgenograms showed a destructive lesion in the eighth thoracic vertebra, which was interpreted as a metastatic lesion. There was an almost complete block in the myelogram at T8. A decompressive laminectomy disclosed a lesion of the body of T8, with some involvement of the lamina on the left at that level and tumor partially surrounding the dura. Removal of enough tumor to effect a decompression was carried out and the pathologic sections showed benign giant cell tumor. This was subsequently given roentgen ray treatment and there has been no further growth of tumor. The patient has remained ambulatory and free of pain since that time and in the past year has undergone cardiac surgery for mitral stenosis.

SUMMARY AND CONCLUSIONS

1. A series of 22 cases of metastatic lesions to the spine and its contents has been reviewed. Two of these had direct metastases to the spinal cord.

2. With the exception of terminal cases of metastatic cancer, patients who are beginning to develop paraplegia from metastatic lesions to the spine should be subjected to decompressive laminectomy before becoming paraplegic.

3. Of the patients who were paraplegic before surgery, none have recovered neurologic function postoperatively and the length of life after surgery averaged about four months.

4. Of the ten patients not paraplegic before surgery, seven had useful survival periods varying from four months to five

years following surgery. Surgery cannot be expected to relieve all pain or to cure the primary disease, but the ambulatory patient with metastatic cancer is a much happier patient than a paraplegic patient with metastatic cancer.

5. The roentgen appearance of destructive lesions in the spine is not always specific for metastatic disease. Two illustrative cases, one of fibrous dysplasia and one of benign giant cell tumor, are presented. In one case, the decompressive laminectomy resulted in further accentuation of the neurologic picture; in the other case a useful, long term survival has been obtained.

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■ Two explanations for some of the results of a section of a lateral half of the spinal cord may be proposed, as regards sensibility. Either it may be imagined, as it has been by several German physiologists, that the gray matter has the power of transmitting sensitive impressions in such a manner that one lateral half of this substance is sufficient for the two sides of the body, or that the conductors of sensitive impressions decussate in the spinal cord, so that those which come from the left side of the body pass into the right side of the spinal cord, and vice versa. The hypothesis of the Germans may explain the fact that sensibility persists on the side of the section, but it is proved to be absolutely inadmissible by the fact that there is anesthesia on the opposite side.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Dystonic Amyotrophy

Dystonia and Muscular Atrophy

I. S. Freiman, M.D. and J. Luwisch, M.D.

RECENTLY we have had the opportunity to observe and study two patients who presented an unusual clinical syndrome. Both patients were males and both manifested dystonia combined with marked generalized muscular atrophy. We have been unable to find any report of similar description and therefore deem it worth while to report the findings in these patients.

Case 1.—A 49 year old unmarried Puerto Rican, employed as a kitchen helper, was admitted to Goldwater Memorial Hospital on June 6, 1951. He came to the United States in 1937. About this time he first became aware of involuntary jerking of his arms, which he attributed to nervousness. These movements gradually increased and he began to drop objects from his hands. By 1948 he had considerable weakness of his arms and weakness had also appeared in the legs. In 1950 the movements had become so severe that the whole body was affected and he had to stop work. In 1951 he began to have sudden episodes of falling to the floor without loss of consciousness.

There was no history of abnormal movements in other members of the family. The patient's father and mother were first cousins. A sister did not walk until three years of age and seems to have had hydrocephalus. One child of the patient's paternal uncle was reported to have "palsy" and was confined to a wheelchair, but was not available for examination. Another child of this uncle had "something wrong" with his ankles.

The physical examination disclosed two outstanding features: a more or less constant involuntary motor disorder and generalized muscular atrophy. Atrophy involved the entire musculature so that the torso was thin, the limbs were very thin, shoulder and pelvic landmarks stood out prominently, and the temples and cheeks were excavated (figures 1 and 2). However, atrophy was most marked peripherally, especially in the hands (figure 3) and in the legs. The thighs were much better preserved, and there was a sharp demarcation just above the knees between the thin legs below and the bulkier thighs, giving the appearance of stork legs. Fasciculations were seldom observed and then only during voluntary activity. There was weakness in the hands, especially on extension and less so in the grip. There was marked weakness in elevation of the arms, but this fluctuated so that on some occasions he almost reached the head and at other times he was unable to raise the arms more than 45 degrees. By contrast with the atrophy, he dorsiflexed the feet well, though better on the left. Muscular power at the knees and hips was fair, so that he was able to squat and to rise from the squatting position.

Muscular tone was somewhat reduced but not to any great extent. The right knee jerk was elicited, but otherwise all the tendon re-

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FIG. 1. *Case 1.* Note generalized muscular atrophy and pes cavus.

FIG. 2. Note atrophy of shoulder girdle.

flexes were absent. A Babinski sign was elicited on numerous occasions on the right side. Abdominal reflexes were present. Pes cavus was present bilaterally. Sensation was intact in all modalities. Movements such as finger-to-nose test were erratic, but largely as a consequence of the involuntary movements rather than from true ataxia. However, a cerebellar component could not be completely excluded under the circumstances, especially since the disability became greater with effort.

There was considerable dysarthria, speech being erratic and irregular. Except for the speech difficulty and the excavated temples and cheeks, the cranial nerves were normal. Pupils and pupillary reflexes were normal, as were the tongue and pharynx. Movements of the neck were free but there was an unusual fullness of the neck in its upper half posteriorly. No mass could be felt in this region. The swelling seemed to be related to the bony defect noted in the roentgenograms (figure 4). Mental status was normal. The patient was cooperative and pleasant, and there was no intellectual impairment.

The patient was ambulatory and able to get about for short distances, but he exhibited an extraordinary dancing and twisting gait. Frequently he appeared to collapse suddenly into a squatting position, but he did not fall and very quickly regained the erect position. At times he went through sudden, wild twisting contortions of the body without falling. He would sit down suddenly when he reached a chair as though throwing himself into it. In

FIG. 3. *Case 1.* Advanced atrophy of hands.

FIG. 4. Roentgenogram of neck showing collapse of fourth, fifth, and sixth cervical vertebrae.

all these gyrations there was frequent torsion of the trunk and pelvis. At times there were slower movements of one or another limb, purposeless and not repetitive. At times there were quicker movements of a choreiform pattern. Frequently the head and neck twisted and turned to one side as in spasmodic torticollis, but it was irregular in pattern and sometimes the head was thrown back in sudden hyperextension. At times the back arched to an extreme degree. Spontaneous dorsiflexion of the big toes was noted. Mild grimacing was frequent. At rest, the movements were markedly decreased.

Laboratory studies of urine and blood, blood chemistry, and serology of blood and spinal fluid were all normal. The spinal fluid was normal including the pressure, and the total protein was 13.8 mg. per cent. Liver function tests were normal. Thymol turbidity measured 1.7 units, cephalin flocculation was ± in 48 hours. Total cholesterol was 152 mg. per cent, and cholesterol esters were 120 mg. per cent. Ratio of esters to total was 79 per cent. Urinary output of creatine ranged from 172 to 310 mg. in 24 hours. Urinary creatinine ranged from 794 to 860 mg. in 24 hours.

Slit-lamp examination was negative for a Kayser-Fleischer ring. Roentgenographic studies of the skull were normal. The cervical spine revealed collapse and deformity of C4, C5, and C6, with narrowed but preserved interspaces (figure 4). These changes were interpreted as degenerative in origin and not developmental. There was no platybasia. Electrical reactions were carried out by the Institute of Physical Medicine of New York University College of Medicine and were reported as revealing no abnormality.

Biopsy specimens of deltoid and anterior tibial muscles were examined by Dr. Abner Wolf. His report: "The great majority of muscle fibers are well preserved and of normal size and have normal striations. Some of the muscle fibers are considerably reduced in volume, but show preservation of their striations. An occasional fiber which is reduced in volume shows an increase in stroma nuclei." The findings were interpreted as typical of neuromuscular atrophy.

Case 2.—A 48 year old unmarried Italian man was admitted to Goldwater Memorial Hospital August 24, 1954. His trouble began in 1933 with the onset of involuntary contractions of face, neck, and right arm, with twisting of the head to the right and backward to a marked degree, followed by extension of the entire spine. This went on for a month and then subsided, only to return after several months. This continued until 1937, when attacks of dizziness without loss of consciousness caused him to stop working. In 1940 he was admitted to a hospital where weakness of the left arm was noted, in addition to the above movements which were interpreted as dystonic. In 1946 he was reported to have had weakness of both upper limbs, and the biceps and triceps muscles were found to be decreased in size. The tendon reflexes were active and the plantar response in th right foot was questionably abnormal. In 1948 the patient's arms became progressively weaker. He could rest only by putting his back against the wall or by lying on his back. He was hospitalized several times and laboratory studies were reported as normal. In 1948, in addition to the dystonia, he was found to have marked atrophy of deltoid, biceps, and triceps muscles and to a slight degree the forearm muscles, with marked hypotonicity and fasciculations. There was no motor weakness in the lower limbs. Deep reflexes were active in the upper limbs, and abdominal reflexes were present. Knee jerks were overactive and there was bilateral ankle clonus. Bilateral Hoffmann signs were present but no Babinski sign. Sensation was reported to be intact.

He continued to walk without assistance until May 1953, when he noted generalized weakness and had marked loss of strength in the legs. He has not walked since. On several occasions he experienced difficulty in urination and in October 1953 he was found to have enlargement of the prostate. Prostatectomy was performed at that time.

In 1919 he was ill in bed with influenza for six weeks and was said to have had severe headaches and some delirium for several days. Thereafter he was in good health until the onset of the present illness. He worked in a paint factory until 1937 when illness progressed to the point where he had to quit work. He has never had colic. In 1932 he acquired syphilis and was treated with arsenicals and mercury. Recent serologic reports have been normal.

The patient's father died of asthma at age 74. His mother is 80 years of age, living, and well. One niece, a 13 year old girl, was found to have cerebral diplegia, mild microcephaly, and mental retardation.

FIG. 5. *Case 2.* Note generalized muscular atrophy. FIG. 6 and 7. Extensive atrophy of small muscles of hands. FIG. 8. Note the visible greater auricular nerve.

Examination in August 1954 disclosed more or less continuous torticollis of the neck to the right, with marked hypertrophy of the sternocleidomastoid muscles. The patient was extremely thin (figure 5). He appeared to have generalized muscular atrophy, but the atrophy was especially marked in the shoulder girdle, upper limbs, and hands (figures 6 and 7). He could elevate the arms only slightly. The lower limbs were thin, with moderate muscular atrophy. There was some weakness at the hips and some weakness in flexion at the knees, but extension at knees and ankles was good, whereas flexion at ankles was weak.

At rest there was some torticollis, but the patient was relatively quiet otherwise. He was unable to stand without assistance. When he was placed on his feet and supported, he developed a marked and constantly shifting motor disorder in an irregular pattern, frequently flexing at the waist or exhibiting twisting and torsion of the trunk and pelvis of short duration or extreme sudden hyperextension of the back. These bodily movements subsided for the most part at rest.

The biceps and triceps reflexes were markedly reduced, and there was inversion of the biceps reflex. The knee and ankle jerks were overactive, with some spasticity. There were bilateral Hoffmann, Babinski, and Chaddock signs. The abdominal reflexes were present. The cranial nerves were normal. Pupils were equal and reacted to light. There was loss of vibratory sense in all four limbs to the iliac crests and the elbows and along the vertebral column to T12. Position sense was greatly impaired in both lower limbs, to a lesser extent in the upper limbs. Sensation was intact to pinprick.

When the head was turned to the side the great auricular nerves in the neck became visible (figure 8). Both were enlarged and thickened. The lesser occipital nerves were easily palpable. The ulnar nerves were firm and thickened. On the dorsum of the right hand a

small cutaneous nerve was visible and palpable. The dorsal cutaneous nerves of the feet were thickened and visible. The thickened palpable nerves were not tender.

The mental status was normal. The patient was well oriented and there was no intellectual deficit.

Urinalysis, blood chemistry, and blood count were all normal, as were studies for lead. The whole blood contained 0.04 mg. per cent of lead. The 24-hour urine specimen totaled 3,500 ml. and contained 0.065 mg. of lead. Skull and chest roentgenograms were normal. The blood Mazzini test was negative. Spinal puncture disclosed 20 lymphocytes and a total of 65 mg. per cent. Colloidal gold and serologic reactions were negative. Chronaxie was reported by the department of physical medicine as within normal limits. Deltoid, dorsal interosseous, and thenar muscles responded to 1 ma. of current flow. Electrical reactions were reported as normal. Biopsy was carried out in the deltoid and anterior tibial muscles, and the specimens were examined by Dr. Abner Wolf. The findings were essentially the same as those reported in case 1, though to a more marked degree, and were interpreted as indicating neuromuscular atrophy. Biopsy of an interdigital nerve in the foot showed it to be thickened, and it revealed considerable proliferation of Schwann cells, but no onion like bodies were found.

DISCUSSION

Comparison of these two patients discloses some differences, but the general pattern in both is similar and the similarities outweigh the differences (table 1). Both have a striking dystonia, more evident on activity than at rest. In each there was marked generalized muscular atrophy, which biopsy disclosed to be neuromuscular atrophy. Both manifested pyramidal tract signs, though one had absent reflexes and the second had exaggerated reflexes. Such a pattern of variation in reflexes from absence to increase in association with pyramidal signs is well known in the hereditary ataxias of different types. Only the second patient had sensory changes and these involved the posterior columns, as is frequently the case in neuromuscular atrophy. Neither had ataxia; the inco-

TABLE 1
SUMMARY OF FINDINGS IN TWO CASES OF DYSTONIC AMYOTROPHY

	Case 1	*Case 2*
Age	49	50
Sex	male	male
Age of onset	33	29
Family history	Consanguinity in parents – suggestion of heredopathy	1 case cerebral diplegia
Dystonia	++	++
Generalized muscular atrophy	++++	++++
Tendon reflexes	Right knee jerk present – all others absent	Biceps and triceps decreased – knee jerk and Achilles increased
Babinski sign	Right positive	Bilateral
Pes cavus	Present	Absent
Muscle biopsy	Neuromuscular atrophy	Neuromuscular atrophy
Hypertrophic nerves	Absent	Present
Sensory changes	Absent	Vibratory sense lost to iliac crests and to elbows – position sense impaired in both lower limbs
Liver function	Normal	Normal
Slit-lamp examination	Negative	Negative
Mental status	Normal	Normal

ordination present was thought to be fully accounted for by the involuntary movements. Both had dysarthria, although it was slight in case 2 and this was also attributed to the dyskinesia. Both patients manifested an extrapyramidal disorder of similar pattern, namely dystonia, along with pyramidal tract signs and involvement of lower motor neurons and peripheral nerves. In both patients the illness was initiated by dystonia, and the muscular involvement appeared some years later.

The syndrome of extrapyramidal disorder with pyramidal signs and muscular atrophy brings to mind Jakob-Creutsfeldt disease.[1] In that process, however, mental symptoms are prominent, rigidity is encountered more often than dystonia, patients are more apt to show hypokinesis, and the course is usually rapid. Our patients clearly do not fall into this category.

Wilson's disease was eliminated by the long course, the late onset, the marked lower motor neuron disease, the pyramidal signs, the normal liver function studies, and the absent Kayser-Fleischer ring.[2] All these in the aggregate are unlike the findings in hepatolenticular degeneration.

Dystonia has been reported both as a disease entity and as a symptom of encephalitis or following other etiologic factors such as brain tumor, syphilis, and so on. Our second patient had influenza in 1919, some 15 years before the onset of his present illness, and it may have been encephalitis. Were the extrapyramidal signs present alone, this relationship would be more acceptable. Since the present illness was associated with evidence of pyramidal disease and had such extensive muscular atrophy following a pattern conforming to the hypertrophic neuritis of Déjérine-Sottas and revealing widespread hypertrophy of nerves, encephalitis was deemed unlikely as a causal agent. No other etiologic factor was established in either patient.

In one patient the pattern was that of Charcot-Marie-Tooth disease. He had stork legs and pes cavus and the reflexes were absent for the most part. However, the atrophy was much more extensive and widespread than is usually the case in the peroneal muscular atrophy of Charcot-Marie-Tooth. Also, the onset was somewhat later than usual. But, as the recent report of Brodal and co-workers has shown, this disorder may begin in the later decades.[3] The second patient exhibited widespread hypertrophy of peripheral nerves and marked impairment of proprioceptive sensibility, a pattern characteristic of the chronic progressive hypertrophic neuritis of Déjérine and Sottas. This disorder commonly begins early in life but some reports have described later onset.[4] Furthermore, Déjérine-Sottas disease may run a relapsing course which may account for the fluctuation of symptoms recorded at times in case 2. Neither of these forms of neural atrophy are associated with pyramidal tract signs as they were in our patients, nor are they associated with extrapyramidal signs. There is some opinion which favors the view that these varieties of neuromuscular atrophy are essentially different aspects of the same fundamental disorder. It is of further interest that in both patients the atrophy and weakness were more severe in the arms and shoulder girdle than in the lower limbs.

The family history in both cases is of interest. In the first case there is consanguinity with the occurrence of several disorders, suggestively neurologic,

but we were unable to investigate them. In the second family there appears a niece having spastic diplegia with microcephaly. Instances of this type have been noted in other reports of heredofamilial disease. The pes cavus in case 1 is also an indication of genetic disorder. This suggests that these cases may be based upon defective heredity. If this is true, these syndromes would appear to be sporadic and represent a recessive factor. Search for similar disorders may in time establish the validity of these views.

SUMMARY

1. Two patients have been presented who exhibited similar syndromes.

2. The manifestations included dystonia, generalized muscular atrophy, and pyramidal tract signs, without intellectual deficit.

3. Biopsy disclosed the presence of neuromuscular atrophy in both cases and hypertrophic neuritis in one.

4. One patient's atrophy resembled Charcot-Marie-Tooth disease.

5. The second patient exhibited widespread hypertrophy of peripheral nerves and marked impairment of proprioceptive sense, conforming to the hypertrophic neuritis of Déjérine and Sottas.

6. Findings in the families of both patients suggested a genetic basis for the syndrome.

7. We have designated this syndrome dystonic amyotrophy.

Our thanks are due to Dr. Abner Wolf for his help in interpreting the muscle and nerve biopsies, and to Dr. Henry K. Taylor for his interpretation of the roentgenograms. We wish to thank Dr. S. B. Wortis for his interest and advice.

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■ Fodera was very near discovering that there is a decussation of the sensitive fibres in the spinal cord. He says he has found in some cases, that a section of one of the posterior columns caused a diminution of sensibility in the opposite side of the body; but he states that in other cases he has seen the reverse. He also has sometimes remarked that the section of one of the posterior columns causes hyperesthesia in the same side, and that a section of these two columns produces hyperesthesia in the two sides, but he declares, also, that he has seen the reverse.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Epilepsy and Dupuytren's Contracture

Alex J. Arieff, M.D. and John Bell, M.D.

DUPUYTREN'S CONTRACTURE is a disease primarily involving the palmar aponeurosis of the hand. This condition is observed most commonly in patients who are in the fifth decade and beyond; however, we have observed patients as young as 19 years and in the early twenties. Gordon[1] reported that an examination of 2,705 hospital patients revealed the presence of Dupuytren's contracture in 369 patients, or 13.6 per cent. Mason and Bell found approximately 300 cases in 12,000 surgical hand patients in a 20-year period (table 1). The involvement of the hands is usually bilateral, and most often the involvement of the palmar fascia begins on the ulnar side of the hand along the pretendinous bands of the ring or little finger. Some patients also have fibrous nodules over the proximal internal angeal joints of the fingers in addition to the palmar contracture. A few patients have thickening of the plantar fascia of the foot. Peyronie's disease associated with Dupuytren's contracture has been observed but is rare.

For approximately 15 years there have been isolated reports published associating Dupuytren's contracture with epilepsy. As high as 50 per cent of male patients with epilepsy have been observed with Dupuytren's contractures (Lund, 25 per cent of 171 female epileptics, 50 per cent of 190 male epileptics;[3] Skoog, 42 per cent in 207 male epileptics[4]). This combination is much lower in the female patient. In a recent report Gordon gives an incidence of Dupuytren's contracture in epilepsy of

TABLE 1
INCIDENCE OF DUPUYTREN'S CONTRACTURE

Mason and Bell,[2] 12,000 patients with hand surgery (20 years)	2.5% (300)
Gordon,[1] 2,705 patients in five general hospitals	13.6% (369)
187 patients with arthritis	16.0% (29)
77 patients with diabetes	29.0% (20)
609 patients with tuberculosis	19.0% (109)
630 patients with epilepsy	9.0% (57)
Arieff and Bell, 168 patients with epilepsy	20.0% (32)

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TABLE 2
DUPUYTEN'S CONTRACTURE IN EPILEPSY (INCIDENCE)

1. Lund[3]	50 per cent in males (190)
	25 per cent in females (141)
2. Skoog[4]	42 per cent in males (207)
3. Gordon[1]	9.0 per cent of 630 epileptics
4. Arieff and Bell	20.0 per cent of 168 epileptics
Severe cases	12.0 per cent of 168 epileptics

only 9 per cent, but in other chronic illnesses a higher percentage (for example, 16 per cent in arthritis, 29 per cent in diabetes, and 19 per cent in tuberculosis).[1]

We examined 168 patients with epilepsy, of whom 32 or 20 per cent showed very mild questionable to definite contracture. If the mild cases are omitted there are 20 unquestioned cases, or approximately 12 per cent. This is far less than the 50 per cent reported by Skoog (table 2).

In over 300 patients who have had surgical treatment for Dupuytren's contracture, a history of epilepsy was elicited in only four patients.[2]

The cause of Dupuytren's contracture has not been established. Males present themselves for treatment about ten times more frequently than females. A high percentage of patients give a family history of Dupuytren's contracture. Skoog reports this incidence as 44 per cent.[4] Occupation seems to have no bearing on the condition, for patients come from all walks of life. In the occasional patient a history of a single trauma or repeated trauma may be obtained; however, this history usually does not appear valid to explain involvement of the uninjured hand or foot as well. The concomitant occurrence of diabetes, gout, or arthritis does not appear to have an outstanding relationship. Most authors state that Dupuytren's contracture is observed mainly in the white race. We have observed the disease in four Negroes, one of whom has been under treatment for epilepsy for many years. One 19 year old patient, a white male, has also been under treatment for convulsive seizures since early childhood.

We attempted to see if there was any

TABLE 3
FACTORS IN DUPUYTREN'S CONTRACTURE IN EPILEPSY

Sex		
	Skoog[4]	90 per cent males
	Lund[3]	50 per cent males
	Gordon[1]	50 per cent males
	Arieff and Bell	50 per cent males
No correlation with		
a) Occupation		d) Type of seizure
b) Coronary disease		e) Electroencephalographic changes
c) Type of medication		f) Remission of epilepsy (26 of 32)
Age of incidence		
	Gordon	55 to 75 years
	Arieff and Bell	40 to 45 years

correlation of this combination of Dupuytren's contracture and epilepsy (table 3). We found none in our material with respect to sex, occupation, type of medication (phenobarbital has been implicated), type of seizure, electroencephalographic changes, or results of treatment (26 of our 32 patients had a remission of all seizures). Gordon likewise found similarly no correlation including coronary heart disease.

In this group about 33 per cent had abnormal electroencephalographic patterns, which is certainly lower than that observed generally in patients with epilepsy. There was no correlation with the type or etiology of the epilepsy. The median age incidence was between 40 and 45 years; in Gordon's group, however, patients ranged in age from 55 to 75 years. Thus, age seems to be the most significant factor in the development of this syndrome.

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■ Sir Charles Bell is the first biologist who has tried to determine the real place of decussation of the conductors of sensitive impressions in the cerebro-spinal axis. He imagines that it is in a small part of the length of the floor of the fourth ventricle above, and near the crossing of the pyramids, but he does not give any reason in proof of his idea, except the results of a deceptive anatomical dissection, quite in opposition with the results of the important researches of John Reid, of Solly, of Valentine, and other anatomists.

Longet also has tried to show the place of decussation of the conductors of sensitive impressions. He admits that the sensitive fibres, after having passed through the cerebellum, go towards the tubercula quadrigemina, along the processus cerebelli and testes, and that they make their decussation below the tubercles. The erroneousness of this view is pretty evident from the fact that the sensitive fibres do not pass through the cerebellum, so that the fibres, which really seem to make a decussation where the anterior peduncles of the cerebellum coalesce, below the tubercula quadrigemina, cannot be the continuation of the sensitive fibres of the body.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Swelling of the Brain Induced by Anoxia

Ricardo F. S. Edstrom, M.D. and Hiram E. Essex, Ph.D.

CEREBRAL EDEMA, in order to be studied experimentally, has to be produced as well as measured. Few seem to have been able to produce cerebral edema under controllable conditions. The most promising reports in the literature have come from workers using systemic anoxia[1] or microemboli.[2]

To measure cerebral edema is rather difficult, especially post mortem, as we have demonstrated recently.[3] On the other hand, a satisfactory method of measuring cerebral edema in vivo has not yet been perfected, although some valuable inferences have been drawn from observations of the exposed brain surface.[4–10] In view of these contributions it is surprising that so few attempts have been made to record variations in cerebral volume. Indirect recordings via the dural pulse cannot be considered satisfactory for the present purposes.

It proved to be relatively simple to record variations of the volume of the brain of a dog during and after exposure of the animal to anoxia or cerebral microemboli. The present study was undertaken to determine the effects of anoxia, systemic and local, on the volume of the brain, and to gain some information on the nature of the changes in cerebral volume so induced.

METHOD OF RECORDING

Variations in the position of the exposed brain surface relative to the skull were taken as evidence of variations in cerebral volume (unless herniation of brain tissue had occurred). To record these variations a trephine opening 24 mm. in diameter in the skull was made routinely in the right parietal area. A star-shaped opening in the dura was made somewhat smaller than the bony defect. The head of the anesthetized animal was fixed with a clamp, so that the exposed area of the cortex was as nearly horizontal as possible. A rod lifting a lever was arranged to rest lightly on the cortical surface, the end of the lever recording changes in volume on a smoked rotating drum (figure 1). The lever system was balanced so as to cause only minimal trauma, but yet to follow the brain surface faithfully. Several hours of recording usually did not leave a macroscopically visible injury on the cortex.

In some animals (tables 1 and 2) the intracranial pressure in the closed skull

With the technical assistance of W. Arthur Meeker, Walter R. Ogg, and Irene E. Donovan.

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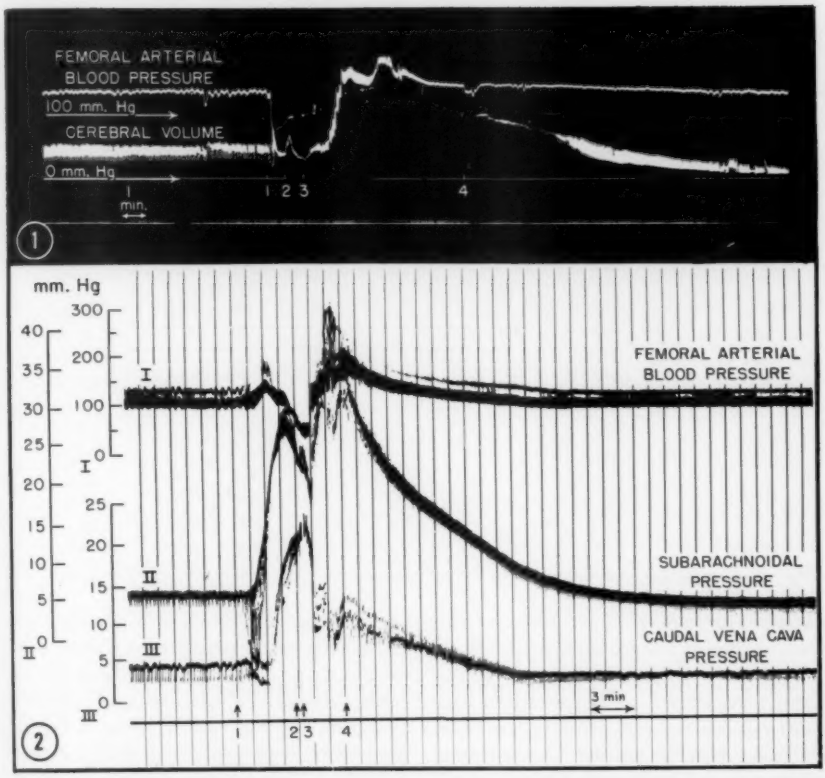

FIG. 1. Variations in femoral blood pressure and cerebral volume. Broad white band in latter tracing reflects amplitude of cerebral pulsations with heartbeats, and fine vertical lines reflect cerebral pulsations with respiration. Exposure to pure carbon dioxide started at signal 1 and ended at 2. Oxygen given by artificial respiration between signals 3 and 4. Note rapid return to less than preexperimental volume (animal 7).

FIG. 2. Variations in femoral arterial blood pressure, subarachnoidal, and caudal vena cava pressure. Exposure to pure nitrogen started at signal 1 and ended at 2. Oxygen given by artificial respiration between signals 3 and 4. Note rapid return of intracranial pressure to preexperimental level (animal 14).

was recorded instead of the changes of cerebral volume. These animals were placed on the right side, and a suboccipital puncture was performed with a 15-gauge needle. Using a strain gauge[11] and an electric-optic system (photokymograph), a photographic recording of the subarachnoidal pressure was obtained (figure 2). Similarly the arterial (femoral) blood pressure and the central venous (caudal vena cava) pressure and occasionally the intracranial venous (torcular Herophili) pressure were recorded photographically. In addition, the femoral arterial blood pressure was also recorded manometrically on a smoked drum.

The routine anesthetic agent was Nembutal (pentobarbital sodium) given intravenously in an initial dose of 25

TABLE 1

DURATION OF CEREBRAL EXPANSION AND INTRACRANIAL HYPERTENSION AFTER EXPOSURE TO ANOXIA SEVERE ENOUGH TO REDUCE THE MEAN ARTERIAL BLOOD PRESSURE TO 40 MM. OF MERCURY OR LESS

Animal	*Exposure to*	*Cardiac arrest, minutes**	*Record*	*Duration of observation, minutes postanoxic*	*Duration of increased volume or pressure, minutes postanoxic*
1	N_2		Cerebral volume	75	8
2	"		"	90	17
"	"		"	30	11
3	"		"	75	16
4	"		"	120	16
5	"		"	240	19
6	"		"	60	19
"	"		"	60	13
7	CO_2		"	30	11
8	"	1.5	"	90	13
9	"	1	CSF pressure	420	30
10	"	1	"	360	10
11	N_2	6	"	360	Rising
12	"	Moment	"	360	13
13	"		"	390	15
14	"		"	360	21
15	"	2	"	390	33

*That is, arterial blood pressure below 20 mm. Hg and absence of pulsation.

mg. per kilogram of body weight. Later it was given as needed in doses of about 5 mg. per kilogram of body weight. These maintenance doses sometimes caused transitory expansion of the brain or increase in the intracranial pressure. Other anesthetic agents (ether, Chloralose) gave similar effects. Tracheotomy or intubation was done in all animals.

SYSTEMIC ANOXIA

The Stimuli. Systemic anoxia was induced by permitting anesthetized animals breathing normally to inhale pure nitrogen or pure carbon dioxide and to exhale through a valve into the open air. This procedure induced practically no respiratory effort or Valsalva phenomenon, but stimulated the breathing until apnea supervened. The exposure to nitrogen or carbon dioxide was continued until the femoral arterial blood pressure had declined to 40 mm. of mercury (approximate mean pressure) or less. Determinations of oxygen saturation (Van Slyke) in samples taken from the arterial blood during the fall in blood pressure showed a mean value of 5.1 per cent (eight animals, standard error of mean 0.6). The final oxygen saturation in the blood before resuscitation must have been less than this. Further confirmation of the severity of the systemic hypoxia induced was furnished by the fact that a large number of animals died in spite of efforts to resuscitate them. Fifteen animals survived after resuscitation (table 1) consisting of artificial ventilation with oxygen until the arterial pressure returned to preanoxic levels. A number of these animals had cardiac arrest for varying periods of time, in which cases extrathoracic heart massage and intracardiac injections of epineph-

TABLE 2
EFFECT ON CEREBRAL VOLUME AND INTRACRANIAL PRESSURE OF EMBOLI GIVEN VIA THE INTERNAL CAROTID ARTERY

Animal	*Embolic material*	*Rise of brain surface, mm.*	*Rise of CSF pressure, mm. of mercury*	*Duration of observation, minutes*	*Maximal change of blood pressure, mm. of mercury*
16	Oil	4		90	+ 5
17	"	6.5		30	—15
18	"	5		15	+10
19	"	1		30	+ 5
19	"	1.5		60	—15
20	"	0.5		30	0
20	"	3		60	—15
21	"	3.5		90	—60
22	"	5		90	—35
23	"	1.5		60	0
24	"	1.5		30	±30
25	"	0.6		15	±15
26	"		18	60	—15
27	"		25	60	0
28	"		20	60	0
29	"		8	15	0
30	Starch		12	180	0
31	"		65	60	±20
32	"		40	60	0
33	"	3.5		60	—10
34	"	0.5		60	0
35	"	1		60	— 5

We wish to express our gratitude to Dr. J. W. Kernohan for evaluating the histopathologic changes.

rine (1/1,000) in doses of 0.1 cc. were given.

Effects of Systemic Anoxia. One animal surviving six minutes of cardiac arrest induced by inhalation of nitrogen had, on resuscitation, an elevated subarachnoidal pressure and a still higher venous blood pressure in the torcular Herophili. These fell during the first postanoxic hour, the pressure in the torcular falling faster than the subarachnoidal pressure. While the pressure in the torcular normalized, the subarachnoidal pressure increased progressively during the next five hours of observation. The brain was found to bulge through a trephine opening made just before exsanguination. Histologically there was definite cerebral edema of recent origin.

The remaining 14 animals survived respiratory anoxia sufficient to produce circulatory failure and in some cases as much as two minutes of cardiac arrest. By the end of the postanoxic period of observation they did not exhibit any expansion of the brain or increase in cerebrospinal fluid pressure above preanoxic levels attributable to cerebral edema (table 1).

Each exposure to nitrogen or to carbon dioxide was immediately followed by a transitory rise in cerebral volume or intracranial pressure. The peaks of

this rise were always synchronous with or immediately following peak values of arterial or venous blood pressure and consistently followed a definite pattern (figures 1 and 2). This pattern evidently reflects the well-known effects of active and passive congestion of the brain.

As can be seen in table 1, the volume of the brain and the intracranial pressure usually returned to preanoxic levels within 30 minutes after beginning recovery of the arterial blood pressure. There was a noticeable overshoot in this return; the brain consistently continued to shrink, and the intracranial pressure usually continued to decrease below preanoxic levels, both reaching a minimum within one hour after the beginning of recovery from anoxia. The second return to preanoxic levels did not follow a uniform pattern.

Comment. Apparently the cerebral anoxia in the 14 animals exposed to almost lethal systemic anoxia never became severe enough to cause cerebral edema. But the findings in the one animal, surviving six minutes of cardiac arrest induced by hypoxia, supported the idea that anoxia is capable of causing edematous brain swelling, provided the local anoxia in the brain is severe enough and the animal survives it.

LOCAL ANOXIA

In order to induce a more severe anoxia of the cerebral tissue, emboli were given.

The Stimuli. Embolizing material was injected via the internal carotid artery in 20 animals. For this purpose the left internal carotid artery was cannulated routinely (that is, contralateral to the cranial trephine opening). The common carotid artery on the left side as well as its other branches at the bifurcation level were tied off. The embolizing material consisted of peanut oil in doses of 0.01 cc. for each kilogram of body weight or corn starch U.S.P. in doses of 1 to 5 mg. per kilogram of body weight. The latter was given as a suspension in less than 1 cc. of saline solution. A few cubic centimeters of saline solution were used to flush the embolizing material through tubing and larger vessels. As a control, a similar dose of saline solution always preceded the injection of the embolizing material. Table 2 lists the types of emboli given to the 20 animals.

Effects of Local Cerebral Anoxia. Microemboli in the form of starch or oil always caused a very rapid increase in cerebral volume, beginning within one minute after the injection and continuing progressively for hours or until the brain tissue protruded through the dural opening. The initial part of this expansion usually took place in the absence of any noticeable change in systemic arterial or venous blood pressure. Later most animals showed changes in respiration and blood pressure, often apnea or circulatory failure.

The initial rapidity of the brain swelling after embolization was striking, but the swelling was not always reflected immediately in the intracranial pressure. The latter always exhibited a gradual rise over hours after the emboli were given.

Hypertonic solutions of sucrose (50 per cent in doses of 2 to 3 cc. per kilogram of body weight), given intravenously to 15 animals at varying times after the embolic material had been administered, failed in every case to reduce the brain volume or the intracranial pressure to preembolic levels, nor could any more than transitory (less than one hour)

effects of the sucrose be noted.

Widening of the dural opening once the cerebral tissue protruded always caused a further protrusion, thus differing from the well known local swelling of cerebral tissue occurring with incarceration.

Microscopic sections of some of the brains exposed to emboli showed varying degrees of local extracellular edema, but other brains similarly exposed showed no extracellular edema at all, although the swelling observed and the postembolic period were similar. The technic used did not permit a reliable evaluation of intracellular edema.

Comment. Admittedly anoxia is but one effect of embolization, but this method has the advantage of not inducing brain swelling or increase in intracranial pressure secondary to changes in systemic blood pressure. The cerebral swelling observed in our experiments after the emboli is most likely the effect of cerebral edema, extracellular or intracellular, as well as local vasodilatation. Probably all three factors are involved, but on the basis of the evidence obtained the relative importance of each cannot be assessed.

The histologic picture of cerebral edema and that of anoxic sequelae in the brain are very similar, as was pointed out by Perret and Kernohan[12] and later by others.[13–16] Among the very first histologic manifestations of cerebral anoxia[16–18] as well as edema[15,16,19] is an accumulation of fluid within the cells. Scheinker[15] has demonstrated that even at this early stage macroscopic signs of brain expansion ("tumefaction") are evident. This may explain the apparent discrepancy between the swelling observed and the degree of histologically evident extracellular edema found in our experiments.

Thus a significant part of the rapid and progressive swelling of the brain observed in our experiments after embolization must be attributed to intracellular accumulation of fluid.

SUMMARY AND CONCLUSIONS

Fourteen dogs under pentobarbital sodium anesthesia survived respiratory anoxia severe enough to give a decrease in blood pressure below 40 mm. of mercury and as much as two minutes of cardiac arrest. These animals did not exhibit any noticeable swelling of their brains or increase in intracranial pressure clearly attributable to cerebral edema within several hours after the anoxic episode. But one animal surviving a longer period of cardiac arrest (six minutes) caused by inhalation of nitrogen later showed a progressive elevation of the intracranial pressure. Histologically there was evidence of cerebral edema.

Local anoxia of brain tissue, induced by oil or starch emboli, consistently caused a very rapid swelling of the brain and an increase in the intracranial pressure in the absence of any obvious systemic hemodynamic change (20 animals). A significant part of this swelling may be attributed to intracellular accumulation of fluid. There was, also, in some of these brains histologic evidence of extracellular cerebral edema.

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■ As a general conclusion, we will say that the conductors of sensitive impressions, at their arrival in the spinal cord, either enter directly the central gray matter, or go up or down a little way in the posterior columns, and also, most likely, in the posterior gray cornua, and in the posterior part of the lateral columns, and entering afterwards the central gray matter, by, or in which, the impressions conveyed by these two sets ascend towards the encephalon.

I will add, that many experiments, some of which are related to this lecture, prove that the restiform bodies, which are the continuations of the posterior columns, seem not to give passage to any of the conductors of the sensitive impressions of either the various parts of the trunk and limbs, or of the head, and that, therefore, the cerebellum, with which the restiform bodies are connected, does not receive from them any of such conductors.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Nature and Significance of Pentosuria in Neuromuscular Disease

Donald B. Tower, M.D., Ph.D., Edmund L. Peters, B.S. and Milton A. Pogorelskin, B.S.

2. CHROMATOGRAPHIC STUDIES

Examinations by paper chromatography were carried out on 43 specimens of 24-hour urine from 21 patients by the methods outlined above. Both two-dimensional and one-dimensional chromatograms (totaling 19 and ten specimens, respectively) were run for nine of the patients. Ten specimens from another nine patients were run in two dimensions only, and four specimens from the other three patients were run in one dimension only. In many cases a single specimen was run in duplicate or triplicate. Ten of the patients had muscle disease clinically while the remainder did not.*

Identification of the carbohydrates present in the urine specimens was accomplished by reference to the behavior of known samples chromatographed under the same conditions. The Rf values in each dimension for glucuronic acid, glucose, lactose, galactose, xylose, fructose, arabinose, xylulose, ribose, ribulose, rhamnose, and desoxyribose were verified by individual runs as well as with mixtures. The means of Rf values obtained in each dimension for each compound are plotted in figure 4. These mean Rf values show good correspondence with values obtained by others using essentially the same solvent systems and conditions.[25,27,49,51] For completeness, the Rf values for mannose and lyxose taken from the literature[49,51] have also been plotted but were not verified experimentally. The Rf values of the ketoses (fructose, xylulose, and ribulose), run in mixtures with other carbohydrates, were further verified by differential visualization of spots with the orcinol-trichloracetic acid reagent.[58] Examples of two-dimensional chromatograms of mixtures of known samples visualized with p-anisidine-HCl and with orcinol-trichloracetic acid are shown in figures 5A and B, respectively.

In addition to the use of Rf values for identification of unknown spots, mixtures of urine plus known samples of the compounds suspected were chromatographed together in selected instances. It is generally accepted that coincidence of un-

*Identification of cases (from tables 5–8) are as follows: *Both*—W.Bu., W.Cl., E.G., D.Bu., L.J., R.Ro., H.B., F.G., and D.T.; *Two-dimensional only*—M.A., J.N., O.M., M.St., N.A., J. Bi., T.F., S.L., and E.P.; *Single-dimensional only*—M.Sc., E.N., and H.C.

The first part of this paper was published in the January 1956 issue of NEUROLOGY (6:37-49,1956).

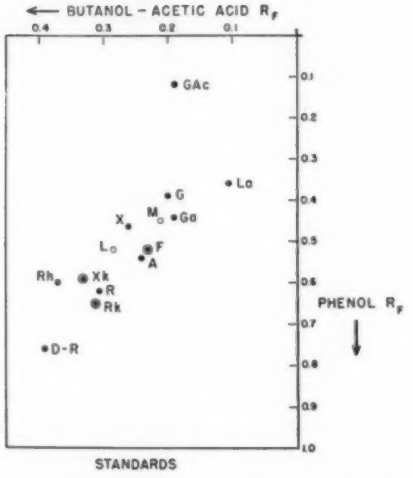

FIG. 4. Plots of mean Rf values experimentally determined in water-saturated phenol and butanol-acetic acid-water as solvents for authentic samples of 12 carbohydrate compounds (●). Values from the literature[49,51] are indicated by ○ for carbohydrates not experimentally verified. Ketoses, experimentally verified by both specific and general color reagents, are indicated by ⊙. Key to abbreviations used is the following:

GAc = glucuronic acid	A = arabinose
G = glucose	L = lyxose
La = lactose	Xk = xylulose
Ga = galactose	R = ribose
M = mannose	Rk = ribulose
X = xylose	Rh = rhamnose
F = fructose	DR = desoxyribose

Point of application of the sample mixture is indicated at the upper right corner. Photographs of representative chromatograms from which this plot was constructed are reproduced in figure 5A and 5B.

known spot with the known sample spot is proof of identity in most cases.[65] The use of specific or differential color reagents, together with examination of spots visualized under daylight and ultraviolet light, provided further evidence of the identity of unknown spots.

The results of two-dimensional chromatography of 29 24-hour urine specimens from 18 patients are illustrated graphically in figure 6. Where more than one specimen from a single patient was chromatographed, the Rf values for each spot detected have been averaged and plotted as a single value. A total of eight carbohydrate compounds were identified from this group of specimens. Presence of glucose, xylose, arabinose, and ribose was definite. In addition spots corresponding in position to lactose and galactose were present in some specimens. Identifications of the two other spots encountered have tentatively been made as glucuronic acid (or closely related uronide) and desoxyribose. The presence of fructose in a few specimens was suspected on the basis of specific spray reagents for ketoses, but the spots were too faint for positive identification. No spots corresponding in position to xylulose or ribulose were detected in a number of duplicate chromatograms of

FIG. 5. Two-dimensional chromatograms with Rf scales for each solvent, water-saturated phenol (Ph) and butanol-acetic acid-water (B-Ac). Point of application of samples is indicated by + in the upper right corner and the direction of solvent runs by arrows. Key to abbreviations used for identifying spots is given in figure 4. *A*. Chromatographed sample of a mixture of authentic standards, all in a concentration of 0.1 μM. (except for xylulose, 0.15 μM., and ribulose, 0.08 μM.). Visualization of spots was with p-anisidine HCl reagent. *B*. Duplicate of the same chromatogram in *A* with visualization of spots by the ketose-specific orcinol-trichloracetic acid color reagent. *C*. Chromatogram of a deionized aliquot of a 24-hour urine specimen from patient R.Ro. (diagnosis: multiple sclerosis) with spot visualization by p-anisidine HCl. No ketoses were deteced by orcinol spraying of a duplicate chromatogram. *D*. Similarly chromatographed sample from patient W.Cl. (diagnosis: progressive muscular dystrophy). No ketoses were detected by orcinol spraying of a duplicate. (The Rf scale for phenol is incorrect and should be shortened so that e.g. G (= glucose) is at Rf = 0.4). All chromatograms were photographed at the same reduction (the degree can be gauged by the fact that the solvent front for phenol (Ph = 1.0) was of the order of 15 to 18 inches from the point of sample application in every case).

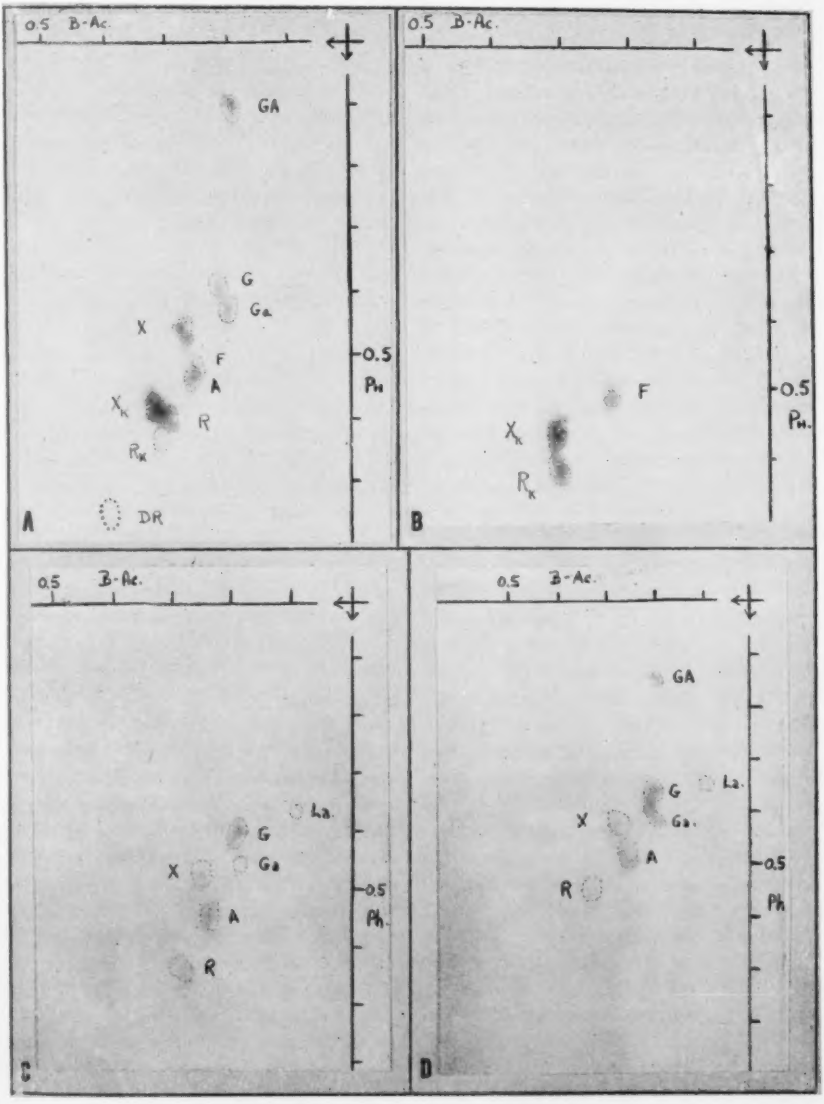

FIG. 5. Legend appears on opposite page.

urine sprayed with the specific orcinol-trichloracetic acid reagent. Three urine specimens were concentrated four times by means of a flash evaporator, deionized, and chromatographed in two dimensions. Again no spots corresponding to xylulose or ribulose were detected, but a definite spot corresponding to fructose was present in all three. Futterman and Roe[63] isolated xylulose, ribulose, and sedoheptulose from pooled normal human urine concentrated 300 or more times. The amounts per milliliter of urine which they report are probably at or below the level of sensitivity of the spray reagent used in this study, even if no losses or degradation occurred during the concentration procedure. It seems clear that appreciable amounts of ketoses are not present in 24-hour urine specimens from patients with or without muscle disease.

The Rf values for each sugar obtained from chromatograms of urine specimens vary to some degree as shown in figure 6. This finding is consistent with the behavior of known samples when chromatographed. The enclosure of all values for a given compound within dotted circles is based upon a similar method of graphic recording used by Wolfson and co-workers,[25] who published data depicting the degree of variations of 75 per cent of the Rf values for each of a number of carbohydrate compounds. Thus, in a study of the present type, the size of the circle enclosing the individual Rf values gives further indication of the probable identity of spots visualized in chromatograms from a number of different specimens. The large circles for glucuronic acid(?) and desoxyribose suggest that these spots may not all represent the same compound. This is likely in the case of those tentatively designated as glucuronic acid in figure 6, since other uronides, notably galacturonic acid, exhibit very similar Rf values.[49,51] The identity of the spots so designated with desoxyribose is probably more certain, since there are few if any other carbohydrates which might be found in animal tissues or fluids which exhibit Rf values close to those for authentic desoxyribose or for the spots detected in the urine chromatograms. In addition the fluorescence of these spots with the p-anisidine-HCl reagent, when examined under ultraviolet light, is similar to that of authentic desoxyribose, which exhibits a brilliant white fluorescence under these conditions.[56]

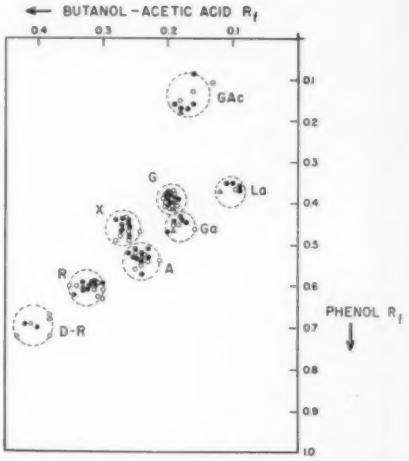

FIG. 6. Plots of the mean Rf values observed with water-saturated phenol and butanol-acetic acid-water as solvents for carbohydrate compounds detected in deionized aliquots of 24-hour urine specimens from 18 patients. Each symbol for a given compound represents the Rf value (or means of several) observed on two-dimensional chromatography of urine from one patient. Patients with myopathies and other muscle diseases are indicated by ●, those with no muscle disease by ○, and one patient (N.A.) with muscle involvement secondary to generalized disease by △. Point of application of samples and abbreviations used are the same as in figure 4. Spot groups identified as a single compound are enclosed within dotted circles (see text).

From the data summarized in figure 6 it is clear that the majority of the 18 patients studied excreted four carbohydrates, glucose, xylose, arabinose, and ribose, in detectable quantities. Some of the patients also excreted a uronide (?-glucuronic acid), lactose, galactose, desoxyribose, and probably fructose. Inspection of the plotted data fails to reveal any difference in the *patterns* of excretion by patients with muscle disease compared to those for patients with no muscle disease, insofar as glucose, xylose, arabinose, and ribose are concerned. Since specimens from both groups of patients exhibited the other less frequent carbohydrates, no differential significance can be attached to these either. It is apparent that the total free aldopentose excretion per 24 hours, determined quantitatively, represents the sum of a mixture of the three naturally-occurring aldopentoses, xylose, arabinose, and ribose. These findings are consistent with reports by others[10,11,23,24,26,63] that man and the rat normally excrete glucose, arabinose, xylose, and ribose in the urine. It should be emphasized that the form of the sugar excreted cannot be determined, since both D- and L- forms behave identically when chromatographed. It is not possible, therefore, to state whether or not the pentoses detected are the naturally-occurring forms and whether or not they are the same forms in every case. Two representative chromatograms made from patient urine specimens are illustrated in figure 5C and D.

Since it is unreliable to attempt to estimate relative quantities from two-dimensional chromatograms, single-dimensinal runs were used for this purpose. Experimentally it was found that, with water-saturated phenol as the solvent, satisfactory separation of glucose, xylose, arabinose, and ribose could be obtained by running the chromatograms for 24 hours. Aniline hydrogen phthalate was used as the reagent for visualization of the spots because it is less likely to detect interfering sugars and because of the distinct color difference it exhibits between aldopentoses (red) and other carbohydrates (yellow to yellow-brown.)[50,51] In all but three cases studied portions of the same deionized urine aliquot were run simultaneously in two-dimensions to confirm the identification of the spots present in the single-dimensional run and to rule out any major interference from other carbohydrates with similar Rf values in water-saturated phenol.

Estimation of the relative proportions of xylose, arabinose, and ribose present was made by the method of Fisher and co-workers[59,60] as detailed in the section on methods above, using calibration curves of spot area (weight) against logarithm of concentration illustrated in figure 2. The results of analyses on 14 24-hour urine specimens from 12 patients are given in table 12. Representative tracings made from some of these chromatograms are illustrated in figure 7. The relative proportions of ribose excreted by patients with muscle diseases are clearly significantly higher than the excretion by patients with no muscle disease. No difference in the proportions of xylose excreted by the two groups was found.

It would be incorrect and misleading to convert these proportional data in actual quantities excreted for quantitative comparisons between one patient and another. However, examination of the results in table 12, together with other quantitative data, suggest that

TABLE 12
SEMIQUANTITATION OF PENTOSES—SINGLE DIMENSION CHROMATOGRAMS

Patient	*Clinical Diagnosis*	*ARABINOSE Estimated μM./Spot*	*XYLOSE* †	*RIBOSE* †
W.Bu.	Muscular dystrophy	0.087	0.1	3.0
W.Cl.	Muscular dystrophy	0.045	0.3	2.8
*M.Sc.	Muscular dystrophy	0.01	tr.	3.5
E.N.	Muscular dystrophy	0.025	0.3	1.2
E.G.	Myotonia dystrophica	0.039	0.3	4.4
D.Bu.	Myasthenia gravis	0.040	0.2	3.7
*L.J.	Myopathy (late)	0.042	0.3	2.0
H.C.	Multiple sclerosis	0.007	0.5	0.0
R.Ro.	Multiple sclerosis	0.157	0.2	0.25
H.B.	Chorioretinitis	0.042	0.0	0.6
F.G.	No disease	0.045	0.0	0.35
D.T.	No disease	0.025	0.3	0.5

† Units, referred to μM./spot of arabinose = 1.0
* Duplicate determinations

excretions of arabinose and xylose were probably of the same order in all patients, regardless of clinical diagnosis. Thus, the increased excretion of pentoses in myopathy patients can be attributed largely to an increase in ribose excretion, in substantiation of the original conclusions of Minot and co-workers[15] (even though the basis for their conclusion rested upon a non-specific test). However, all but one of the patients studied excreted some ribose and all excreted one or both of the other two aldopentoses, so that the increase in ribose excretion in myopathies is a matter of degree and not an absolute abnormality.

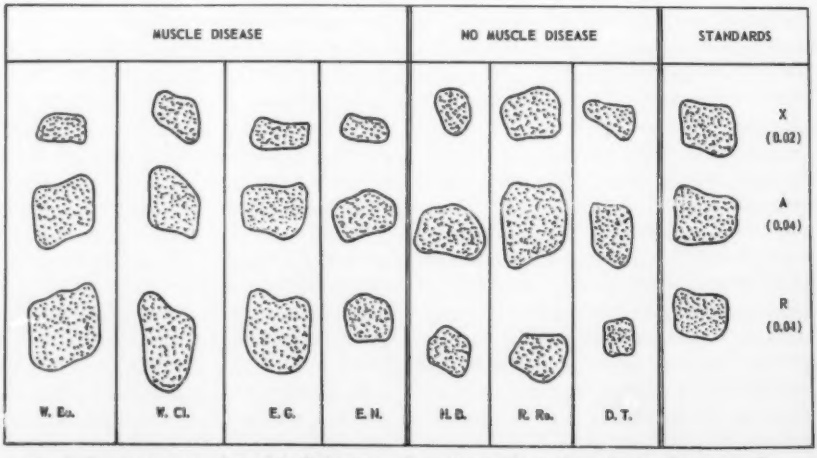

FIG. 7. Representative tracings of single-dimension chromatograms for semiquantitation of pentoses. Comparative sizes of spots (traced from originals) for xylose (X), arabinose (A), and ribose (R), detected by the aniline hydrogen phthalate color reagent on single dimensional (phenol) chromatograms of deionized aliquots of 24-hour urine specimens from a representative number of patients in table 12. Comparative tracings of spots of standards, chromatographed as mixtures in the same manner, are shown in the extreme right-hand column (concentrations given in parentheses in μM.).

TABLE 13
EFFECT OF DIET ON PENTOSE EXCRETION
Subject: D.T., ♂, 35 (80 kg.)

DAY	DIET	24-Hour Urine Volume (ml.)	Pentose Excretion per 24 hr. (μM.)	Chromatographic Semiquantitation† XYLOSE	ARABINOSE	RIBOSE
1	Regular	1020	573			
2	Regular	880	573			
3	Regular	950	486	1.1	2.0	0.6
	(Av.)	(950)	(547)*			
4	Fruit-free	—	—			
5	Fruit-free	—	—			
6	Fruit-free	1230	226			
7	Fruit-free	1130	213	0.3	1.0	0.5
	(Av.)	(1180)	(220)			
8	High-fruit	1280	2250	5.0±	3.9	0.6

† Referred to arabinose = 1.0 on day 7. Size of glucose spot essentially same in all three. Identity of spots verified in two dimensions.
* Patient R.F., ♂, 20 (55 kg.) excreted 606 μM. in 24 hours on regular diet.

Assessment of the effect of diet on pentose excretion by the foregoing methods is shown for one subject in table 13. Taking data obtained during the fruit-free period as the baseline, pentose excretion on a regular diet was more than double, the excess apparently accounted for mostly by xylose and arabinose. High fruit intake resulted in a ten-fold increase in total pentose excretion, representing mostly increased xylose excretion. It is probable that diets high in arabinose would show it to be excreted in greatest proportion. These results do reemphasize the importance of a fruit-free regime for the study of other types of pentosuria.

The effects of starvation on urinary excretion by the rat have been studied by Futterman and Roe.[63] Glucose, xylose, arabinose, and ribose continued to be excreted during starvation (as well as several ketoses, excepting fructose, in concentrated specimens). The authors felt that the origin of the pentoses and others excreted was unlikely to be exogenous (diet residual or from intestinal flora) but probably represented endogenous pentoses from breakdown of tissue complexes. In cases of essential pentosuria, studied by paper chromatography of urine specimens from eight patients, Barnes and Bloomberg[27] observed xylose and arabinose in addition to xylulose in all specimens examined (the technic did not permit visualization of ribose). Urine specimens from normal subjects studied by the same technic showed no detectable pentoses. Since the urine aliquots applied to the chromatograms by Barnes and Bloomberg[27] were about one-tenth the volume necessary in the present study to obtain satisfactory visualization, it is suggested that not only is there an abnormal amount of xylulose excreted by patients with essential pentosuria but there is also an increased excretion of xylose and arabinose. No specimens from such cases have so far been available to test this possibility.

3. CORRELATION WITH CLINICAL STATUS

Clinical ratings of the severity of involvement of each patient with muscle disease were obtained from ward neurologists who were unaware of the pentosuria results. The ratings were based upon the duration of disease, rate of progression, degree of muscle involvement and incapacitation, and the patho-

TABLE 14
POTASSIUM EXCHANGED IN 22 HOURS PER KG. BODY WEIGHT†

		No Muscle Disease	*Muscle Disease*
Number		26 { M-20, F- 6 }	24 { M-12, F-12 }
Mean age (yrs.)		30	30
Mean weight (kg.)*		64	49
Mean Ke/kg.††		22.7	16.5
Standard deviation		2.42	3.97
Standard error of mean		±0.47	±0.81
No muscle disease	S.E.D.	0.94	
vs.	t	6.6	
Muscle disease	N	48	
	P	< 0.001	

† Data derived from Shy 62.
†† Ke = Potassium *exchanged* in 22 hrs. = $\frac{\mu C\ K^{42}in - \mu C\ K^{42}\ ex}{\frac{\mu C\ K^{42}/L\ urine}{mEq\ K^{39}/L\ urine}}$

* Significance of difference in weight not high ($P \cong 0.05$)

logic appearance of muscle biopsy specimens. Comparison of the clinical ratings with the amounts of pentose excreted per 24 hours (either total or per kilogram body weight) showed no correlation whatsoever. Myopathy patients with high pentose excretions often were rated clinically as minimally involved or vice versa, and patients who were comparable clinically were often very different in terms of amounts of pentoses excreted. Perhaps the lack of correlation is not so surprising when the many variables and uncertainties which are inherent in clinical estimates are considered.

A more objective criterion seemed to be the amount of residual functional muscle. Creatine and creatinine excretions were not reliable in the present series because meat- or purine-free diets were not used. However, 22 of the patients in this investigation had also been included in studies of the amounts of potassium exchanged by patients with or without muscle disease, using the radioisotope of potassium, K42. From data obtained in this study by Shy and co-workers,[66] the potassium *exchanged* by respective patients in 22 hours per kilogram body weight* was calculated. Table 14, taken from their data, summarizes their findings in terms of Ke/kg. for patients with no muscle disease compared to those with some form of muscle disease, including 22 of the patients studied in the present paper. Because of the variations in age, sex, and body build it was considered desirable for purposes of comparison to use Ke/kg. rather than total Ke, restricting the patients included to homogeneous populations by the same criteria discussed previously. The difference of the means of Ke/kg. of the two groups in table 14 is statistically significant ($P < 0.001$). Shy and co-workers[66] concluded that the potassium exchanged represented a parameter of residual functional muscle mass because the body skeletal muscle serves as the major potassium reservoir and because they found the supply of

*As defined by Shy and co-workers,[66] the potassium exchanged,

$$Ke = \frac{\mu C.\ K^{42}\ in - \mu C.\ K^{42}\ ex}{\frac{\mu C.\ K^{42}/L.\ urine}{mEq.\ K^{39}/L.\ urine}}$$

potassium to muscle and its turnover rate in muscle to be the same for dystrophic and normal muscle. Thus, a reduction in the amount of potassium exchange would reflect a reduction in functional muscle mass of comparable amount, since fat and collagen which replace the diseased muscle fibers do not contain or turn over significant amounts of potassium.

Data on the potassium exchanged per kilogram body weight and the free aldopentose excretion per 24 hours per kilogram body weight for 22 adult patients in the present study are shown in table 15 and plotted in figure 8. Four of the patients were excluded from calculation of the significance of the correlation. They are omitted from table 15 but are plotted in figure 8 in parentheses. One patient (M. Sc.) with muscular dystrophy was excluded because of obesity; the other three cases excluded were diagnosed as myopathy of late onset which did not seem classifiable with the remaining cases.* The significance of this correlation is statistically high ($P < 0.001$). From the data, the regression coefficient of the linear plot has been calculated to be -0.38 (± 0.03) and, using this value, the theoretical slope has been plotted in figure 8.

These results suggest that the degree of elevation of pentoses excreted per kilogram of body weight is proportional to the extent of reduction in functional muscle mass (as reflected by potassium exchanged per kilogram body weight). Thus, the increased pentose excretion by patients with myopathies apparently is a result of muscle disease and would not be detectable until significant muscle dysfunction or wasting has occurred. The fact that cases of muscular atrophy participate in this correlation is consistent with the above interpretation, but it is not clear why cases of myasthenia gravis should also participate. The deviation of cases of myopathy of late onset from the correlation cannot be explained, but several possibilities are suggested. The three patients do not appear to be overweight, which could account for such a deviation. Alternatively, reduction in potassium exchanged might precede the onset of increased pentose excretion, or the rate of progression in these cases might be too slow to produce a significant daily rise in pentose excretion whereas reduced muscle mass would still be reflected in reduced potassium exchanged.

Pursuit of such speculation is not likely to be helpful when based upon studies of urine, which at best can only reflect

*The seven children in this study for whom both sets of data were available have not been included in table 15 or figure 8. The higher level of pentose excretion by the younger patients as a whole (tables 9 and 10) would require a separate plot and correlation. Trial plots suggested that a similar linear relationship between Ke/kg. and pentose excretion /24 hr./kg. exists parallel to that for the adults, but the number of young patients is too small to test this satisfactorily and there were no children without muscle disease for whom both sets of data were available for comparison in such a correlation. The data for these seven children with muscular dystrophy are as follows:

Patient	*Ke/kg.*	*μM Pentose/24hr. /kg.*
J. A.	10.6	7.7
Da. B.	26.8	7.1
Do. B.	30.6(?)	8.4
P. Cl.	20.7(?)	13.0
J. F.	16.1	9.5
J. Sa.	10.6	10.5
O. Z.	20.5	9.2

The two questionable Ke/kg. values occur in patients who had considerable muscle wasting and may conceivably represent erroneous observations or may represent a difference in the pathologic process or stage compared to the other patients in this group.

TABLE 15
CORRELATION OF PENTOSE EXCRETION WITH POTASSIUM EXCHANGED

Patient	*Diagnosis*	*Ke/kg.*†	*Pentose μM./24 hr./kg.*
M.A.	Muscular dystrophy	16.3	6.3
A.H.	Muscular dystrophy	10.5	7.6
J.L.	Muscular dystrophy	16.1	7.8
W.M.	Muscular dystrophy	11.9	9.5
E.N.	Muscular dystrophy	22.5	6.1
R.R.	Muscular dystrophy	19.0	7.5
A.W.	Muscular dystrophy	19.9	4.2
S.T.	Myotonia dystrophica	18.1	4.4
K.G.	Myositis ossificans	22.8	6.5
E.J.	Myasthenia gravis	11.7	8.7
J.N.	Myasthenia gravis	18.0	5.8
J.Ba.	Muscular atrophy, ? Cause	12.9	8.2
D.H.	Muscular atrophy ? Cause	19.5	5.3
O.M.	Muscular atrophy ? Cause	16.3	8.6
N.A.	Diss. lupus erythematosus	22.5	5.0
F.H.	Granulomatous uveitis	23.0	2.8
E.K.	Cerebral seizures	21.0	3.0
J.St.	Cerebral seizures	24.4	3.8
r = -0.746	N = 16	P < 0.001	

† Potassium *exchanged* per kg. body weight in 22 hrs.

at a distance events which may be occurring in muscle. Further elucidation of these observations should properly be applied directly to studies of muscle metabolism of pentoses.

DISCUSSION

Two principal biochemical abnormalities have already become associated with muscle diseases. Creatinuria coincident with muscle wasting (either primary or secondary) is a well established abnormality.[67] Alterations in muscle electrolytes, notably potassium, are now recognized to occur in muscle diseases, related also to muscle wasting as demonstrated by Shy and co-workers.[66]

To these a third abnormality can now be added. The original suggestions that pentosuria occurs in association with

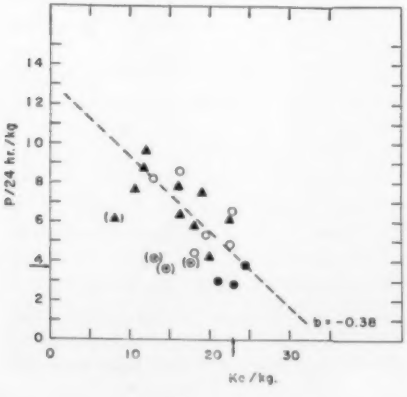

FIG. 8. Correlation of excretion of free aldopentoses (μM./24 hrs./kg. body wt.) with potassium exchanged (Ke/kg. body wt.) by adult patients derived from table 15. Patients with myopathies (muscular dystrophy, myotonia, etc.) are indicated by ▲, those with myasthenia gravis or muscular atrophy by ○, and those with no muscle disease by ●. Three patients with myopathy of late onset (see text) are included indicated by ⊙. Points in parentheses have been excluded from calculation of correlation data (see text). The value of the regression coefficient, b, has been calculated from data in table 15, and the theoretical slope of the regression line (dotted line) is derived from this value by the formula $y = a + bx$. Mean values for the group with no muscle disease (tables 10 and 14) are indicated by arrows on the respective coordinates.

muscle disease[12,15–18] have been substantiated by the present study. Quantitatively, significantly higher amounts of free aldopentoses, apparently mostly as ribose, are excreted by patients with muscular dystrophy, myotonia, and probably myasthenia gravis and gross muscular atrophy. Again a relationship to muscle wasting is suggested.

Recently a fourth set of abnormalities has been added by the studies of Dreyfus, Schapira, and Schapira[68–70] on enzymatic activities in normal and myopathic muscle. These studies were suggested by the observations of Sibley and Lehninger[70] who found elevated serum aldolase activity in two cases of muscular dystrophy. Schapira and co-workers[69] confirmed this observation in studies on 41 cases of myopathy, whose mean serum aldolase activity was ten times that of 17 normal controls. Elevations of lesser degree were found in sera from patients with other neuromuscular diseases. Accordingly these investigators determined the activity of four enzyme systems concerned with glycolytic utilization of carbohydrates in both normal and dystrophic muscle samples.[68,70] The activity of phosphorylase catalyzing the interconversion of glucose-1-phosphate and glycogen in dystrophic muscle was 35 per cent of normal activity. Phosphoglucomutase catalyzing the conversion between glucose-1- and glucose-6-phosphate gave an activity in dystrophic muscle which was one-half of normal. Aldolase activity, concerned with several interchanges among fructose-6-phosphate, triose-phosphates, and pentose-phosphates, was reduced in dystrophy to about 30 per cent of normal. And overall glycolysis, as measured by lactic acid production from glucose, was reduced to about one-quarter of the normal activity in the dystrophic muscle samples. As indicated by the experimental details, these studies were well carried out. In particular the authors were careful to express all enzyme activities per gram of noncollagenous protein, which obviates the errors introduced when the well known increases in collagen and lipids in dystrophic muscles are not compensated for. Dreyfus and associates[70] concluded that probably all enzymes of the glycolytic scheme were affected in the course of myopathies but that, while these findings might account for some of the clinical symptoms, they do not necessarily represent the biochemical lesion. Whether these abnormalities are also present in other types of muscle disease must await further study, but the serum aldolase results suggest that there may be enzyme abnormalities in some of the other types of diseased muscle.

For the interpretation of these four abnormalities in muscle diseases, a brief consideration of carbohydrate metabolisms is in order. Present knowledge of the paths by which hexoses and pentoses are utilized and metabolized have been summarized in figures 9 and 10. These figures have been modified from Horecker[72] and supplemented by data from other sources.[73] Beginning with glucose or glycogen (figure 9) two principal pathways of metabolism are now known. One is the familiar Meyerhof-Embden glycolytic scheme through fructose, the triose stage (glyceraldehyde) and on to pyruvate (or lactate) and oxidation in the Krebs cycle or its alternatives.[74] The other is the so-called alternate pathway of glucose oxidation or the hexose monophosphate shunt of Warburg, Lipmann, and Dickens[75–77] via phosphogluconate to ribulose and ribose. These two sys-

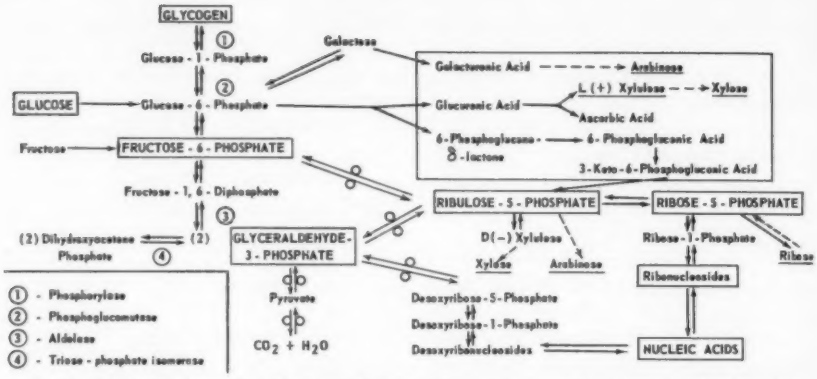

FIG. 9. Principal pathways for glucose and glycogen utilization in mammalian tissues via glycolysis (on the left) and via hexose monophosphate shunt (on the right). Reactions concerned with incorporation of pentoses in nucleic acid syntheses are shown at the lower right. Reactions not occurring in skeletal muscle are enclosed in the box. Where intermediates in a reaction are not given, this is designated by the conventional arrow with attached circle. Enzymes concerned in some of the important steps are indicated. This figure has been modified from sources summarized by Horecker,[72] Racker,[73] and Umbreit.[74]

tems exist side-by-side in liver, kidney, and other tissues, but in skeletal muscle the stages of the second system between glucose-6-phosphate and ribulose-5-phosphate are not present,[78–81] as indicated by the boxed portion in figure 9. However, the interchanges at the fructose and triose stages with pentoses are present in muscle, many of the reactions being catalyzed by aldolase. Present knowledge of the numerous reactions at this important metabolic crossroads between pentoses and hexoses or trioses are detailed in figure 10, modified from Horecker.[72]

Basically the multiplicity of reactions serves to provide the tissue with sufficient alternatives, by-passes, and "storage" points to satisfy many changing metabolic requirements and conditions. For present purposes the schemes can be simplified by considering three important reaction sequences. 1) The first of these is the mechanism by which glucose supplied to muscle can be converted via fructose-6-phosphate to ribose-5-phosphate, or via triose-phosphate (plus an active two-carbon fragment from ribulose-5-phosphate) to desoxyribose-5-phosphate, for nucleoside and nucleic acid synthesis and tissue structure.[82–86] The ability of tissues such as muscle to accomplish this without an exogenous supply of pentoses is important and economical. 2) The second important reaction is the converse of the first, the mechanism by which endogenous or exogenous ribose- or desoxyribose-phosphate derived from nucleic acid and nucleoside breakdown can be salvaged by conversion to fructose-6-phosphate.[87–89] The breakdown need not be pathologic but simply in the course of normal tissue turnover and repair. This mechanism is important in conservation of energy and structural units within the tissue. 3) The third important reaction involves the mechanism for splitting pentose (as ribulose-5-phosphate) into a triose-phosphate and "active glycoaldehyde," a two-carbon fragment utilized for synthesis of important metab-

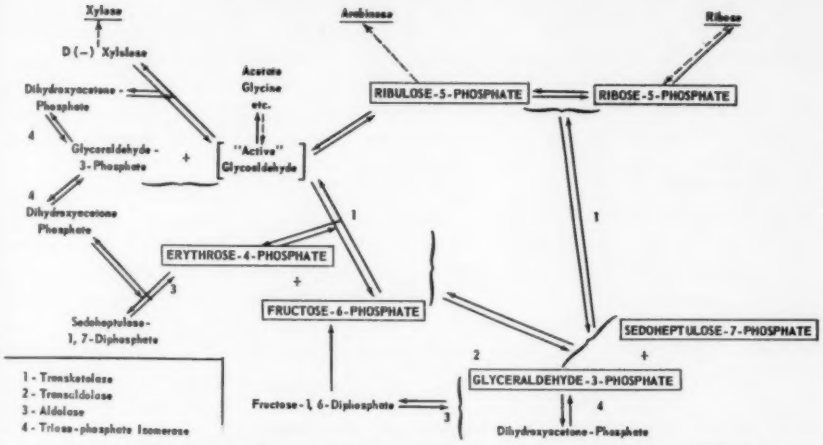

FIG. 10. Detailed diagrammatic representation of reactions concerned with interchanges between pentoses (and related compounds) and hexoses or trioses in mammalian tissues. Enzymes identified with these reactions are indicated. This figure has been modified from Horecker.[72]

olites in the tisue such as glycine.[90,91] These are vital areas of tissue metabolism, any derangement of which can be expected to have many consequences.

There are several possible sources of the pentoses found normally in human urine and for the increased amounts occurring with muscle disease. Two sources are well established. One is from pentoses ingested in the diet. Pentoses occur widely in foods from plant and animal sources,[22] certain of which on ingestion can produce marked increases in urinary pentoses[8] (table 13). In essential pentosuria, the source of the L(+) xylulose excreted is endogenous, associated with glucuronic acid metabolism.[6] Apparent traces of L(+) xylulose may be excreted normally and such excretion can be enhanced by feeding glucuronide.[6] The system for production of glucuronic acid from glucose and for utilization of glucuronide in detoxification and the like is found in liver but apparently not in muscle, so that the source of L(+) xylulose is nonmuscular. Possible sources for arabinose from galacturonic acid or ribulose-5-phosphate, for xylose from D(−) xylulose (derived from ribulose-5-phosphate), and for ribose from dephosphorylation of ribose-phosphates have been indicated in figures 9 and 10. The structural configurations of these pentoses are shown in figure 11. None of these side reactions are known to occur in vivo, although some have been induced in vitro. Since the complete metabolic scheme in figure 9 is known to occur in liver, kidney, bone marrow, and other tissues but is incomplete in skeletal muscle,[81] if such side reactions did occur, the tissue of origin would not necessarily be muscle. The urinary excretion of xylose, arabinose, ribose, and in smaller amounts ribulose, xylulose, and heptulose by rats on a starvation regime[63] suggests that for this species these sources or analogous sources can function to some extent.

For ribose the most likely tissue source

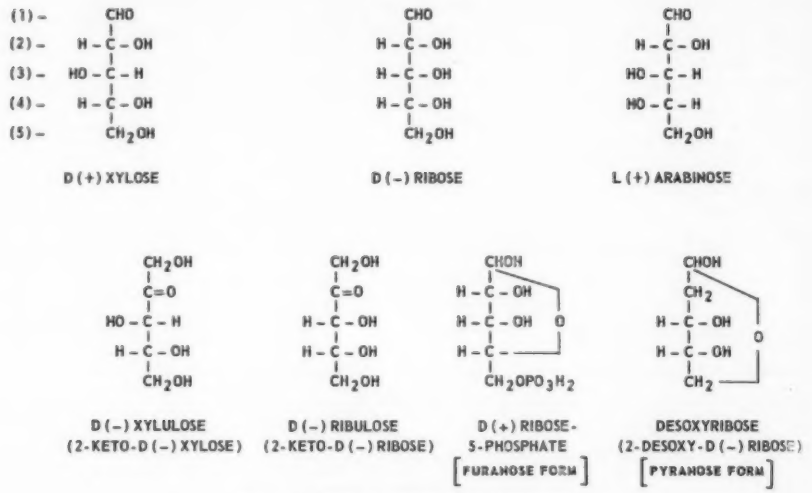

FIG. 11. Structural configurations of pentoses.

is from tissue breakdown, the degradation of nucleic acids and nucleosides with splitting off of the pentose moiety. Muscle apparently cannot utilize exogenous ribose-5-phosphate directly, but only as adenosine or some other nucleoside source and no ribokinase has been demonstrated in muscle to permit utilization of ribose.[91] Thus, ribose-phosphate or ribose (which could be liberated by phosphatases during tissue breakdown) could easily be rejected for excretion. Rises in serum pentose levels following experimental trauma,[92,93] increased levels of free aldopentoses in cerebrospinal fluid, blood, and urine following cranio-facial injuries in man,[94] and increased pentose excretion experimentally induced by cold exposure or by administration of thyroid[10] or cortisone[11] are all consistent with the above mechanism.

In myopathies an absolute reduction of muscle aldolase activity in the residual muscle to less than half its normal activity[67,69] would seriously interfere with pentose to hexose interconversions (figure 10). If, in addition, muscle is independently being broken down, the liberated pentoses could not be conserved by the remaining muscle tissue for lack of aldolase and excretion of excess ribose could occur. Alternatively, the block or partial block interposed by reduced aldolase activity would markedly reduce production of pentoses from available glucose or other sources such as nucleosides. If both possibilities operated simultaneously, the net effects would be a cycle supported by tissue breakdown (either normal or abnormal) on one side and failure of normal routes of supply on the other.

In this connection it is of interest that Ord and Stocken[94] have recently demonstrated experimentally a reciprocal relationship between creatine liberation from skeletal muscle and blood glucose

supply to the muscle. It is easy to substitute for lowered blood glucose the inability of dystrophic muscle to utilize a normal supply of glucose, which, from the observations of Ord and Stocken,[94] might also be expected to liberate creatine in the same fashion as normal muscle deprived of its supply externally.

From the foregoing discussion it is apparent that a logical pattern is beginning to emerge which could account for the abnormalities demonstrated to occur in association with muscle disease. Present evidence would favor the interpretation that all are results of the disease process and may not be related directly to the underlying biochemical lesion causing the disease. Whether or not this proves to be the case, the leads now available make it possible to approach the problem of disordered muscle metabolism more rationally and with more reasonable expectation of uncovering the basic mechanisms concerned.*

SUMMARY

1. The quantitative excretion of free aldopentoses in 230 24-hour urine specimens from 55 patients with and without muscle disease has been studied by the para-bromaniline acetate method. All patients were on fruit-free diets.

2. The mean excretion of total free aldopentoses per 24 hours per kilogram body weight were: 1) by patients with no muscle disease 3.6 μM. for adults and 5.5 μM. for children (under 15 years of age), and 2) by patients with myopathies 6.6 μM. for adults and 9.6 μM. for children. Differences between the means of the two groups of adults or of children were statistically significant in both cases.

3. No increase in total free aldopentose content was found after acid-heat hydrolysis of a number of specimens from both groups.

4. Identities of the pentoses excreted were established by 29 two-dimensional paper chromatograms of 24-hour urine specimens from 18 patients. All samples were deionized before being run by descending chromatography with water-saturated phenol and butanol-acetic acid-water as solvents. Visualization of carbohydrate spots was by means of aniline hydrogen phthalate, p-anisidine HCl, and orcinol trichloracetic acid reagents. Criteria for identification comprised Rf values in each dimension, coincidence of urine spots with those of added standards, and appearance of spots with differential color reagents visualized both in daylight and in ultraviolet light.

5. Eight carbohydrate compounds were identified in urine specimens. The majority contained glucose, xylose, arabinose, and ribose. A few exhibited spots identified as lactose, galactose, desoxyribose, and a uronide (?glucuronic acid). No ketoses were detected in regular or concentrated specimens with the possible exception of fructose. No differences in the patterns of carbohydrates excreted between the group with and that with-

*Since completion of this manuscript, a symposium on muscular dystrophy has appeared (Am. J. Phys. Med. Feb. 1955). Data presented therein, particularly by R. W. Gerard (pp. 279-80), T. S. Danowski (pp. 281-85), and G. Schapira and associates (pp. 313-19) are pertinent and consistent with the above.

Since acceptance of this paper, a report by Ronzoni on co-workers has been published (Neurology 5:412, 1955) on ribosuria in muscular dystrophy. These authors found no free ribose in paper chromatograms of urines from 20 dystrophic and ten control patients, but observed, after hydrolysis, ribose in most specimens, presumably representing nucleotide-bound ribose. The failure of these investigators to detect free ribose, using aliquots three- to ten- times those used in the present study, is in contrast to results reported here and in previous reports[10,11,23,24,26,68] and is probably due to the method of treatment of specimens prior to chromatography. The use of urease in particular has been found to interfere seriously with subsequent demonstration of certain carbohydrates.[91] Preliminary treatment of specimens with the exception of deionization is unnecessary and may result in erroneous findings.

out muscle disease were apparent.

6. Semiquantitation of the aldopentoses excreted was carried out by the spot-area method on single-dimensional (phenol) chromatograms of 14 urine specimens from 12 patients, using standard calibrations obtained under the same conditions. Arabinose predominated in urine specimens from the group with no muscle disease, whereas ribose appeared to be significantly higher in specimens from the group with muscle diseases. There was no difference in the amounts of xylose excreted by the two groups.

7. The findings suggest that patients with muscular dystrophy, myotonia dystrophica, myasthenia gravis, and muscular atrophy (?cause) excrete significantly higher amounts of free aldopentoses in 24 hours, largely accounted for as ribose, than patients with diseases such as multiple sclerosis, spinal cord disease, cerebral seizures, and uveitis.

8. No correlation of these findings with clinical status (based upon duration of disease, rate of progression, degree of muscle involvement and disability, histopathology, and electromyography) could be established.

9. Good correlation of μM. pentoses excreted/24 hrs./kg. body weight with functional residual muscle mass (as measured by potassium exchanged per kg. body weight [Ke/kg.] as data obtained in a separate study) was demonstrated for 22 adult patients for whom both sets of data were available. The coefficient of correlation was highly significant statistically. This finding suggests that, as residual functional muscle mass is reduced, the urinary excretion of pentoses, mostly as ribose, increases.

10. The implications of these findings both in terms of sources of the pentoses excreted and in terms of pentose metabolism in muscle are discussed.

The authors wish to express their thanks to Dr. G. Milton Shy for kindly making patients from the clinical neurology service, N.I.N.D.B., available for this study, together with data on his studies of potassium exchanged, and for his advice and interest during the investigations. Control patients from the clinical ophthalmology service, N.I.N.D.B., were kindly made available by Dr. Ralph W. Ryan. The assistance of Dr. William C. Curtis in determining the purity of carbohydrate standards, in preparing certain of the organic reagents, and in carrying out concentrations of urine specimens for this study has been invaluable. Finally the success of these investigations has in large measure been due to the care in collection of specimens and supervision of fruit-free diets by the N.I.N.D.B. nursing service and dieticians.

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DIAGNOSTIC NOTE

Limited Value of Carotid Pulse in Diagnosis of Internal Carotid Thrombosis

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A PALPABLE INTERNAL carotid pulse in the neck or pharynx does not vitiate a diagnosis of internal carotid artery thrombosis. When the diagnosis appears to be appropriate by history and neurologic examination, the finding of a palpable carotid pulse only points to the need for further study by angiography. The following cases illustrate this. Each patient had good carotid pulsations on the side contralateral to the paralyzed extremities, but on angiography each was demonstrated to have an internal carotid thrombosis, the first at the level of the carotid siphon, the second at the origin of the internal carotid.

CASE REPORTS

Case 1.—A 29 year old white sergeant was involved in a fight on December 31, 1954 and was knocked out. When he arrived at a dispensary and recovered consciousness, he noted weakness and numbness of the left arm and leg. During the course of the day this weakness progressed, though he was alert and without headache, and he was admitted to the U.S. Army Hospital at Frankfurt on January 1, 1955.

Examination revealed an oriented patient with a severe left hemiparesis. The blood pressure was 124/76. The pupils were equal, the fundi normal, and the visual fields full on confrontation testing. The deep tendon reflexes were hyperactive on the left, with positive toe signs. There was no sensory deficit. Palpation in the neck revealed normal carotid pulses bilaterally. A lumbar puncture yielded clear fluid containing one lymphocyte per cu. mm., and 41 mg. per cent protein. The blood serology was negative.

The presenting picture was one of left-sided stroke without evidence of hemorrhage or of increased intracranial pressure. Strength began to return in the left lower extremity to a limited degree in a few days. A right carotid angiogram done on January 17 disclosed an occlusion of the internal carotid artery just distal to the origin of the posterior communicating artery (figure 1). The posterior cerebral artery filled; the anterior and middle cerebrals did not. The angiogram was repeated on February 3 with identical findings.

The patient made a gradual, limited recovery and became ambulatory, but with a spastic, hemiparetic gait. There was little return of function in the hand.

Case 2.—A 31 year old sergeant of Puerto Rican descent, while on field maneuvers on June 8, 1955, developed a right-sided headache, fell down twice, and then lost consciousness. He was admitted to the U.S. Army Hospital at Nurnberg in a semicomatose state. On examination the blood pressure was 100/80. There was a left hemiplegia and a left lower facial paralysis. The tongue deviated to the left. The abdominal reflexes were absent on the left. The deep tendon reflexes were equal bilaterally. The pupils were equal, the fundi normal. Lumbar

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FIG. 1. Right common carotid angiogram. One sees filling of the internal carotid and posterior cerebral arteries. The internal carotid is occluded beyond the origin of the posterior communicating artery.

FIG. 2. Right common carotid angiogram. The external carotid and its branches are filled. There is an occlusion of the internal carotid a few millimeters beyond its origin, and a heavy concentration of Diodrast is seen in the short, blind segment.

puncture yielded clear fluid at 200 mm. pressure, containing 4 lymphocytes per cu. mm., and 22 mg. per cent protein. The blood serology was negative.

By June 11 he had roused from his stupor and was beginning to take oral fluids. Hyperactivity of the deep tendon reflexes on the left became manifest. By June 13 his sensorium was clear. There was dysgraphesthesia in the left hand. Muscle examination two days later revealed return of weak hip flexion and knee extension, but the left upper extremity and the left foot remained paralyzed. An electroencephalogram was normal. The carotid pulses in the neck were normal. There was no intracranial bruit. Pharyngeal palpation was done after spraying with 2 per cent Xylocaine solution. The carotid pulse was normal on each side.

On June 11 a right common carotid angiogram was done and the internal carotid found to be thrombosed at its origin (figure 2). The external carotid filled well and appeared large. There was no filling of the anterior or middle cerebral arteries.

DISCUSSION

A qualification needs to be imposed on the importance of palpation of the carotid pulse in the detection of occlusion of the internal carotid artery. When an occlusion is suspected and the carotid pulse is found to be absent on pharyngeal palpation, the diagnosis would appear to be unequivocal.[1,3] The finding of a pulse, however, is not sufficient reason to abandon a strongly suspected diagnosis, but only points to the need for further study by angiography.

There are two explanations for the existence of a pharyngeal carotid pulse in proved cases of complete occlusion of the internal carotid. In the first place, pharyngeal palpation will naturally fail to be of diagnostic significance when the thrombosis is at the carotid siphon, as in case 1. The siphon was found to be the site of predilection in 16 of 97 cases of internal carotid thrombosis surveyed by Johnson and Walker,[2] the remaining occlusions having occurred in the most proximal part of the internal carotid. Secondly, it appears that a pulse that is palpable through the lateral pharyngeal wall does not necessarily originate from the internal carotid artery. In case 2 a complete occlusion of the internal carotid at its origin was demonstrated by angiography, yet the carotid pulse was easily palpated both in the neck and pharynx. The external ca-

rotid, in spite of its more lateral position in the neck, is apparently capable of transmitting a pulse which can simulate that of the internal carotid in the pharynx.

For these reasons, then, the finding of normal carotid pulses in the neck and pharynx only makes the diagnosis of internal carotid occlusion more elusive, but not untenable. The sign appears to be specific if the pulse is absent, but inconclusive for diagnosis if the pulse is present.

SUMMARY

A suspected diagnosis of thrombosis of the internal carotid artery is probably unequivocal if the carotid pulse is found to be absent in the neck and pharynx. The presence of a pulse in the neck and pharynx, on the other hand, does not in itself invalidate a strongly suspected diagnosis and is indeed compatible with the diagnosis, but throws the burden of proof on angiography.

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■ The following experiment was the first which led me to the conclusion that there are fibres of the posterior roots descending in the posterior columns: I introduced a very sharp bistoury between the posterior and the anterior parts of the spinal cord, and by cutting from above downwards, or in the opposite direction, I separate a part of the length of the posterior columns of the cord from the anterior parts of this organ. This being done, I divide transversely and in its middle the part of the posterior columns separated from the anterior parts of the spinal cord, so as to obtain two segments, one superior, the other inferior. The superior I will call cephalic segment, and the other caudal segment. Now, when there are some little parts of the posterior gray horns and some fibres of the posterior roots attached to these segments, we obtain this apparently strange and surely unforeseen result, that not only the caudal segment is sensitive, but that it seems to be more sensitive than the cephalic segment. But whatever may be the real amount of sensibility in these two segments, there is one capital conclusion to be drawn from this experiment, and this is, that a number of the conductors of sensitive impressions in the posterior roots pass in the posterior columns, in which some go upwards toward the encephalon (centripetal or ascending fibres), while others go in the opposite direction, i. e., downwards or backward (centrifugal or descending fibres).

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

CASE REPORT

Peripheral Neuropathy Associated With Multiple Myelomatosis

Edwin Clarke, M.D., M.R.C.P.

THERE ARE MANY unsolved problems concerning peripheral neuropathy* and one of the most important is that of etiology. Recently its association with carcinoma of the bronchus has been established,[11,18,19,26] although the occurrence of peripheral nerve involvement with cancer was first mentioned before the turn of the century.[3,23,32] A similar complication has been reported in leukemia[17] and in Hodgkin's disease.[12] It is the purpose of this paper to describe polyneuropathy associated with multiple myelomatosis.

LITERATURE

There is very little to be found in the literature concerning this condition. Snapper, Turner, and Moscovitz[38] mentioned it as a complication of myelomatosis but did not describe any cases. Seventeen case reports are available, but only nine can be accepted as verified examples (table 1); of these, only four have been adequately described (cases 1, 2, 3, and 9).

Among the eight which must be excluded is the case of Levison and Møller,[28] for it does not fit into the usually recognized clinical syndrome of "polyneuritis," and Levison's later remarks[27] indicated some confusion of nomenclature. The patient of Neel[33] had a "progressive polyneuritis" but a cord-compressing myeloma complicated the picture. In a case of Davison and Balser,[9] anemia seemed to be an important etiologic factor, a possibility admitted by the authors. Patients of Lawrence and Rosenthal[25] and Lawrence and Wasserman[43] had polycythemia as an additional complication and therefore have been excluded. The three cases of Kurnick and Yohalem,[24] appearing in one of the two articles devoted to this subject, are doubtful examples. The first seemed to have focal root involvement and the third is confused because diabetes mellitus was also present. The second may be a true case, but the role of a spinal lesion is not entirely clear.

To the nine remaining cases another is added, already included in a survey of the neurologic manifestations of myelomatosis.[8]

CASE REPORT

Male, 66. One year of generalized paresthesias with pain and coldness of fingers and toes.

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*Henson and co-workers[19] have used the term "neuropathy" to describe a variety of neurologic conditions, but this seems to be unnecessarily confusing. In the present article "neuropathy" is employed in its usual sense and implies a disease of peripheral nerves.

Severe back pain seven months and leg weakness four months. Findings of a polyneuropathy (with ? peripheral vascular occlusive disease). X-rays, cerebrospinal fluid, myelogram normal. Hyperglobulinemia and erythrocyte sedimentation rate 140 mm. Bence-Jones proteinuria. Abnormal pyruvate metabolism. Survival 15 months. Death. No autopsy.

A 66 year old agricultural agent was admitted to the Radcliffe Infirmary, Oxford, on July 21, 1947.

One year before admission he noticed the gradual onset of "pins and needles" all over the limbs and trunk. The toes and fingers were painful and frequently cold, despite the summer weather. For seven months there had been pain between the shoulder blades, extending to the front of his chest one month later, and having some of the characteristics of root irritation. Four months previously he had experienced difficulty in walking on account of leg weakness, and for two months weakness of the arms had been apparent. He had lost a considerable amount of weight recently.

Examination. His general condition was poor and he was suffering considerable pain. The latter affected the hands in particular and the grip was poor because of it. There was distal weakness in the upper extremities, whereas in the lower limbs it was mainly proximal. Muscle wasting was generalized and the leg muscles were tender. All the tendon reflexes were very sluggish in the upper limbs and absent in the lower limbs; there were no pathologic reflexes. Sensory findings varied, but there was impairment of pain and touch of a stocking distribution in the legs. Varying areas of hyperalgesia could be demonstrated at times. Other modalities were normal.

Movements of the spine provoked pain in the limbs. The peripheral arteries were all pulsating, but the left ring finger was a bluish color and was tender and cold to touch. Blood pressure was 170/100. The heart was normal.

Laboratory studies. Roentgenograms of the skull, spine, chest, pelvis, and long bones were normal. Cerebrospinal fluid: pressure, 70 mm. of water; no block; no cells; protein 25 mg. per cent; other contents normal. Blood: hemoglobin 11.0 gm.; red cells 3.4 million per cc.; white cells 6,000; erythrocyte sedimentation rate 140 mm. in one hour. Proteins: total 8.98 gm.; albumin 2.8 gm.; globulin 6.18 gm. per 100 ml. Urine showed a trace of Bence-Jones protein. Bone marrow (sternum) showed an abnormal content of plasma cells compatible with the diagnosis of myelomatosis. Pyruvate metabolism curve was markedly elevated, with some decrease after giving thiamine and nicotinic acid. A myelogram was normal.

Course. The pain persisted and at times the patient was irrational and noisy. He was dis-

TABLE 1
CASES OF NEUROPATHY ASSOCIATED WITH MYELOMATOSIS

Case No.	*Author*	*Date*	*Sex*	*Age*	*Presenting symptom*	*Total survival*	*Roentgenogram*	*Spinal fluid protein mg.%*	*Outcome*	*Amyloid*
1	Scheinker[38]	1938	M	38	Pigmented skin Numb toes	14 months	—	Normal	Death (autopsy)	Not mentioned
2	Berlin[6]	1946	M	64	Temperature changes and aching in feet	9 months+	Spine, skull, etc. normal	61	?	Not mentioned
3	M.G.H. Case No. 32231[31]	1946	F	51	Aching and burning in fingertips	6 months	Normal	Normal	Death (autopsy)	Present
4	White and Tillinghast[42] Case 3	1950	M	59	Chronic diarrhea	?	Multiple granular bony lesions	—	?	Not mentioned
5	Madonick and Solomon[29] Case 6	1953	M	53	Paresthesias of fingers and toes	8 months+	—	212	Death (?autopsy)	Not mentioned
6	Case 8		M	58	Shoulder pain	1 year+	Normal	71	Death (autopsy)	Of tongue
7	Case 10		M	53	Skin nodules	8 months+	—	72	Death (?autopsy)	Not mentioned
8	Case 14		F	59	Pain right arm	2 years+	Normal	Normal	Death (autopsy)	Generalized
9	Estes and Millikan[15]	1954	F	43	Low back pain	4 months+	Normal	200	?	Not mentioned
10	Clarke	1955	M	66	Paresthesias limbs and trunk	15 months	Normal	25	Death (no autopsy)	Not looked for

charged on August 22, 1947, one month after admission, and returned to his home where he died some months later. An autopsy was not carried out.

COMMENT

Pain was a prominent feature of this man's illness, which is a characteristic of a neuropathy as well as of multiple myelomatosis.

The cold extremities and the color changes of one finger suggest peripheral vascular disease rather than vasomotor disturbance due to the neuropathy. The presence of hyperglobulinemia supports this conclusion, for Berlin[6] in a similar case postulates "capillary embolisms" produced by the abnormal serum proteins. As a spinal cord compressing lesion could not be excluded confidently, a myelogram was carried out. The abnormal pyruvate metabolism indicates peripheral nerve dysfunction.

ETIOLOGY

Scheinker[36] and other authors have suggested that toxic influences are responsible for myelomatous neuropathy. Comparison with other malignant diseases lends support to this hypothesis but, as pointed out elsewhere,[8] the theory of myelomatous toxins affecting the nervous system is open to considerable doubt.

Other possible etiologic factors have been considered, and Berlin[6] thought that hyperglobulinemia, by encouraging intravascular clotting, might be important. However, in only four of the eight patients tested in this series was a high serum globulin found. Similarly, it has been suggested that the Bence-Jones protein may produce the toxic phenomena,[20] but in only five cases out of ten was it present. Associated anemia is a possible factor and it was present in some degree in five of the patients who had blood examinations. It is unlikely that it plays a significant etiologic role for, while it is one of the commonest features of myelomatosis, a peripheral neuropathy is one of the rarest. That a neuropathy secondary to anemia may occur, however, is evidenced by the case of Davison and Balser[9] already mentioned.

It appears that a satisfactory explanation for myelomatous neuropathy is not available, and the theory of toxins does not in any way diminish the obscurity.

PATHOLOGY

Although invasion of peripheral nerves by malignant cells is found in allied diseases such as carcinomatosis[21] and leukemia,[14] it probably never occurs in myelomatosis. Infiltration of spinal roots has been mentioned by Bender[5] and Brownell,[7] but lack of details and doubt concerning the diagnosis arouse suspicion. Petrides[34] depicted invasion of a sympathetic ganglion, but again the diagnosis was in doubt. This phenomenon has likewise never been described in cranial nerves; in fact, Sparling, Parker, and Adams[40] describe an abducent nerve surrounded, yet not invaded, by myeloma cells. These findings are entirely in keeping with the knowledge that myelomatous tissue never extends into the substance of the nervous system.[8]

In only one case of myelomatous neuropathy[36] has there been a pathologic examination of the nervous system. In the peripheral nerves, a parenchymatous degeneration was seen and in the spinal roots, "perineuritis interstitialis scleroticans." These changes appear to be nonspecific.

CLINICAL PICTURE

It is difficult to synthesize the clinical picture because only five of the cases noted in table 1 were adequately described. The age and sex characteristics are the same as in other forms of myelomatosis. The usual features of a peripheral neuropathy are observed, but pain in the limbs, especially in the hands, is an outstanding characteristic. This may take the form of painful paresthesias (case 3), or the pain may originate in the muscles of the extremities so that each movement is painful. Pain in the back such as occurs with the primary disease is also

common (cases 9 and 10). A striking hyperalgesia of the skin has also been remarked upon,[36,39] and symptoms and signs of thoracic root irritation were present in cases 9 and 10. Weakness and wasting, no doubt also part of the generalized disease, are also found in the extremities, and eventually the use of the limbs may become limited. Symptoms may be more severe in the legs (Berlin's[6] patient had bilateral foot-drop: case 9), or in the arms (in case 3 feeding was impossible). The limbs seem to be symmetrically involved. Occasionally indications of peripheral vascular occlusive disease may be present (cases 2 and 10) and it seems that they are due to direct vascular disease rather than to the vasomotor disturbances of a peripheral neuropathy.

In addition, other features of myelomatosis are eventually evident if they are not present at the onset of the disease.

It is important to realize that the first signs of multiple myelomatosis may be a peripheral neuropathy, and this was so in six of the ten cases, including the case described here. The course of the disease is usually rapidly progressive, with relentless increase of all the polyneuropathy features as well as those of myelomatosis and amyloidosis too, if present. In the cases where the total survival period could be estimated, it was usually less than two years and sometimes less than one. Death in one case (case 1) was due to respiratory paralysis, but in the others the generalized disease was probably the immediate cause.

LABORATORY STUDIES

The cerebrospinal fluid was normal in four of nine cases and a raised protein content was detected in five. Although Madonick and Solomon[29] were not able to establish a correlation between spinal fluid abnormality and clinical neurologic features, they suspected that a polyneuropathy could contribute to a high protein level. In only one patient (case 4) was there an abnormal radiologic finding. A normochromic anemia, elevated plasma values with hyperglobulinemia, and a high sedimentation rate were common findings. Bone-marrow biopsy is of greater diagnostic value than a search for Bence-Jones proteinuria. An abnormality of pyruvate metabolism was discovered in one case (case 10).

TREATMENT

Only two patients in this series were treated, one with Priscol (case 2) and one with thiamine (case 10), but the course of the disease was not influenced. As in other manifestations of myelomatosis, therapy is limited and can only be palliative.

DISCUSSION

The incidence of myelomatous neuropathy is not known but is probably more common than generally thought. Recently Madonick and Solomon[29] included three examples among 21 cases of myelomatosis (14 per cent), but this figure is probably too high.

From a consideration of the limited information available, one is able to suggest a possible etiologic agent. It is known that primary amyloidosis may accompany multiple myelomatosis in 15 per cent of cases,[4] and three of the cases in table 1 (cases 3, 6, and 8) had this association. In addition, it is possible that five others (cases 2, 4, 7, 9, and 10) were similar; diarrhea (cases 4 and 9), skin nodules (case 7), and peripheral vascular occlusive disease (cases 2 and 10) are suggestive of this.

A neuropathy produced by primary amyloidosis is now a well recognized entity,[2,10] and it may be that the involvement of peripheral nerves in myelomatosis is due to this process rather than to the primary disease itself.

Unfortunately there is no direct pathologic evidence of this because amyloid has never been looked for in these cases. That it does occur in myelomatosis, nevertheless, was shown by Tverdy[41] who described a paraprotein, probably amyloid, in the ganglia and nerves of the autonomic nervous system in one case. The peripheral nerves

were not examined, but both they and the autonomic system may be affected by amyloid in the same case.[10] Furthermore Ritama and Björkesten,[35] when reexamining pathologic material, found amyloid in the nerves from a case of myelomatosis. It is thought that the amyloid involves the peripheral nerves by either interfering with their blood supply,[22] by direct invasion of cells and nerve trunks,[10,41] or by pressure of amyloid deposits on the nerves. One or more of these mechanisms may produce the clinical picture in myelomatous neuropathy. It is interesting to note the case of Grokoešt and Demartini[16] where, in a case of myelomatosis, amyloid infiltration of tendons produced a typical carpal tunnel syndrome.

Clinical information is also scanty. However, the predominance of pain, especially around the joints, the marked muscle wasting and weakness, the hyperalgesia, the evidence of peripheral vascular occlusive disease, and other features of amyloidosis suggest that the latter may be the etiologic factor. The features of amyloidosis may contribute to the clinical picture of myelomatous neuropathy so that differentiation of the two may be difficult.[31] Snapper and coworkers[38] stated that, in cases of myelomatosis with amyloidosis, the bone roentgenograms are usually normal. This was so in five of the six cases so examined, although in most of them the investigation had not been extensive.

It is possible that in at least some cases of myelomatous neuropathy the accompanying primary amyloidosis may produce the peripheral nerve lesions rather than the primary disease. It may also have occurred in the puzzling case of Senator[37] with multiple cranial nerve palsies, for amyloid was found in the kidney. Knowledge concerning primary amyloidosis is incomplete, but its role in multiple myelomatosis will only be elucidated by a careful search for it in all appropriate cases. Furthermore, Jackson and Slavin[20] reported some success with ACTH in the treatment of primary amyloidosis and, although this substance is known to have little effect upon myelomatosis,[13] it may help to alleviate some of the symptoms of neuropathy if other measures have failed.

CONCLUSIONS

1. Peripheral neuropathy is a rare manifestation of multiple myelomatosis, but it may be the presenting feature of the disease.

2. Pathologic and clinical knowledge is scanty but to the picture of a polyneuropathy are added the features of myelomatosis, with or without primary amyloidosis.

3. Bone roentgenograms are often normal, and the cerebrospinal fluid protein may be increased.

4. It is submitted that accompanying primary amyloidosis may produce the neuropathy rather than the primary disease.

5. It is reasonable to try the effect of ACTH in these cases.

SUMMARY

A peripheral neuropathy ocurring with multiple myelomatosis is described. To the nine acceptable cases so far reported, another is added. Although information concerning the pathology and the clinical picture is inadequate, it is suggested that primary amyloidosis accompanying myelomatosis may be responsible for the peripheral nerve lesions. Clinically, features of a polyneuropathy, which may be the first evidence of the disease, together with myelomatosis and amyloidosis are observed. Treatment has been uniformly unsuccessful, but the use of ACTH is suggested.

The author would like to thank Mr. J. B. Pennybacker for permission to publish his case.

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CASE REPORT

Ependymoma of the Cerebellopontine Angle in an Infant

Joseph G. Chusid, M.D., C. G. de Gutiérrez-Mahoney, M.D. and Thomas Q. Garvey, Jr., M.D.

CEREBELLOPONTINE ANGLE GLIOMAS which resemble other angle tumors in their clinicopathologic features have been described and their origin has been linked with the lateral medullary velum, the thin narrow band of tissue forming the floor and medial wall of the lateral recess of the fourth ventricle. Tumors of this type are so rarely encountered or reported that their characteristics are not widely known. Recent experience with a case in which a papillary ependymoma occupied a cerebellopontine angle prompted the following case study and a review of similar cases in the literature.

REPORT OF A CASE

A five week old male infant was referred for hospitalization because of progressive hydrocephalus. The mother of the boy, an only child delivered without difficulty after a normal full-term pregnancy, stated she first became aware of increased head size at the age of two weeks and thereafter the head appeared to enlarge more rapidly. The child then became irritable and difficult to feed, regurgitating excessively and vomiting frequently.

On admission he appeared well nourished and well developed but was rather irritable and lethargic. The head was symmetrically enlarged, measuring 44.5 cm. in circumference; the anterior and posterior fontanelles bulged moderately. The eyes appeared to be deviated down and inwardly; the pupils were fixed, small, and unreactive to light. The child made no attempt to follow a light with his eyes. He appeared able to move all extremities spontaneously; deep tendon reflexes were mildly hyperactive bilaterally. On the day after admission the lateral ventricles were punctured and clear cerebrospinal fluid under moderately increased pressure was obtained. Dye instilled into the lateral ventricles could not be demonstrated thereafter in the lumbar cerebrospinal fluid. Air ventriculography subsequently disclosed marked symmetric dilatation of the lateral ventricles; the third ventricle, aqueduct, and fourth ventricle could not be demonstrated. A Torkildsen type ventriculocisternostomy was performed on the following day, shunts being established between the posterior horn of each lateral ventricle and the cisterna magna by means of rubber catheters. The child's condition did not improve postoperatively; respirations became suddenly irregular and rapid and he expired approximately 12 hours after operation.

Pathologic findings. The significant findings were confined to the chest and head. There was evidence of confluent lobular pneumonia, subpleural and intrapulmonary hemorrhage, pulmonary edema, and congestion.

Examination of the brain after formalin fixation revealed marked symmetric dilatation of the lateral and third ventricles. An ovoid discrete tumor occupied the right cerebellopontine angle, compressing and distorting the adjacent

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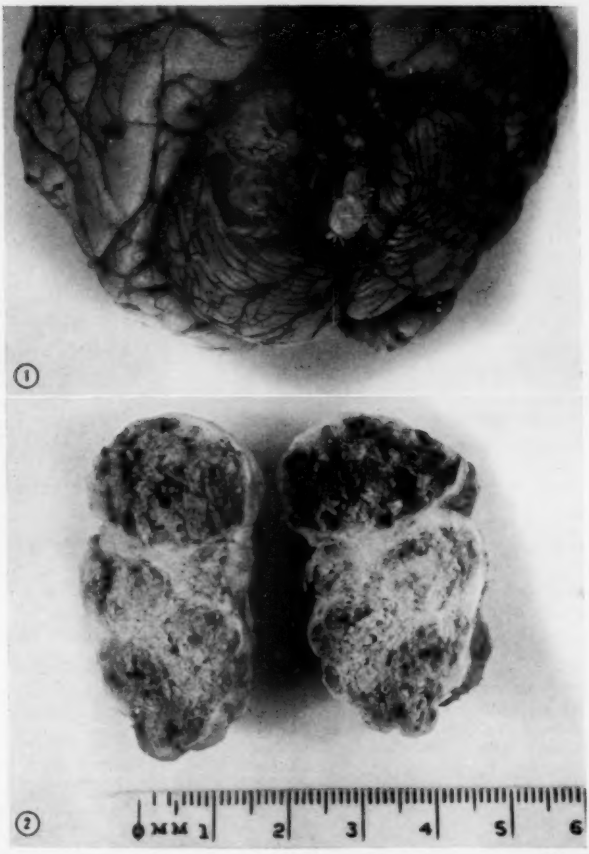


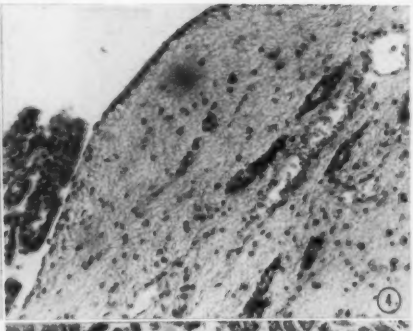
FIG. 1. View of base of brain with papillary ependymoma in right cerebellopontine angle.

FIG. 2. Tumor in cross section (long axis).

brainstem and overlying cerebellum (figure 1). The fourth ventricle appeared compressed and tilted, but was free of tumor; the pons and medulla oblongata were displaced toward the left. The right acoustic nerve was thinned, flattened, and stretched over the superior aspect of the tumor. The tumor measured 4.5 cm. in its long axis (parallel to the brainstem) and 2.5 cm. in cross section (figure 2). Its surface appeared nodular and was yellow-tan in color; cut sections contained granular, gray-pink, lobulated, firm tissue with a more solid appearing thick stroma and encapsulating portion. The tumor had a firm consistency except for its posterior third which felt cystic; it separated quite readily and easily from the adjacent brainstem and cerebellum after gentle teasing and blunt dissection along its dorsal margin, but its precise anatomic site of origin was not grossly apparent.

Histologic examination. The tumor had the microscopic appearance of a papillary ependymoma (figure 3). Tumor cells, ependymal in type and cuboidal in shape with prominent nuclei containing dense chromatin masses, were arranged in papillary manner around a central stroma. Cells of the tumor appeared uniform; mitotic figures were not observed. The tumor had an encapsulating portion which appeared to be similar to the stroma.

Ependymal-lined canals and spaces and collections of ependymal cells were noted in the subependymal zone of the right dorsolateral



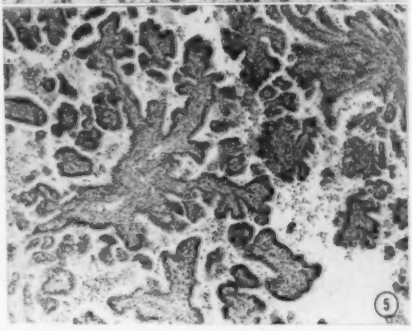


FIG. 3. Section from tumor with appearance of papillary ependymoma. Hematoxylin and eosin stain.

FIG. 4. View of dorsolateral medulla oblongata with ependymal canals and cell collections. Hematoxylin and eosin stain.

FIG. 5. Section through medulla showing pronounced distortion and compression that had been produced by the tumor. Weil stain.

and lateral medulla oblongata extending toward the zone of attachment of the lateral medullary velum (figure 4). Tissue like that on the surface of the tumor was attached to the lateral dorsal edge of the medulla oblongata in the area near the inferior border of the foramen of Luschka (figure 5).

DISCUSSION

The use of the term "velum medullaris lateralis ventriculi quarti," or lateral medullary velum, for the medial wall of the lateral recess has been attributed by Millen[6] to Kernohan,[5] who in turn credits Percival Bailey with suggesting this name. Riley[7] had referred to this area as the "lamella medialis recessus ventriculi quarti." The studies of embryology and morphology by Blake[2] indicated that there is a greater development of nervous matter in the walls of the lateral recess in man than in lower mammals. Both Millen and Kernohan felt that gliomas might arise from local cell rests, emphasizing that the lateral medullary velum often contains glial collections (ependymal cells, oligodendroglia, astrocytes, microglia) and more rarely ganglion cells with their processes. Alexander[1] also stated that the medial wall of the lateral recess of the fourth ventricle might give rise to extramedullary gliomatous tumors, and reported his findings in a case of medulloblastoma and in a case of spongioblastomatous malformation.

The largest and most extensive series of gliomas of the cerebellopontine angle is that described from the Mayo Clinic in the reports of Millen[6] and Kernohan.[5] Of the ten cases in this group eight were ependymomas, and seven occurred in children under age of 11 years.

In many respects the case presented here has features similar to those of the gliomas of the cerebellopontine angle reported by Kernohan and associates. Displacement and

compression of adjacent brainstem and cerebellum without local invasion, stretching of cranial nerves, predilection for children, obstructive hydrocephalus, and ependymoma tumor type were commonly noted. A papillary type ependymoma similar to that in our patient was described in their case 2. As in our case, most of the tumors could be readily separated at post mortem from adjacent brainstem and cerebellum, and the site of anatomic origin was usually not grossly apparent. Thus in case 7 of the Kernohan series (epithelial type ependymoma) it was stated, "The tumor was not attached to the brainstem or to the cerebellum at any place and the fourth ventricle had not been invaded," and in case 8 (cellular ependymoma), "The neoplasm was not attached to the medulla, pons or cerebellum."

The occurrence of a developmental defect or anomaly associated with the formation or elaboration of the lateral medullary velum seems probable in our case. Ependymal-lined spaces or canals were present in the adjacent dorsolateral medulla oblongata, especially near the site of attachment of the lateral medullary velum. These formations were quite different in appearance from the tumor tissue in the cerebellopontine angle which was extramedullary. Such findings were not noted in the other cases referred to above, although similar collections within the normal lateral medullary velum itself are quite common. Since our patient was only five weeks old and his tumor quite large, neoplastic changes probably had started before birth. This infant appears to be the youngest reported with a cerebellopontine angle glioma and the second with a papillary type ependymoma.

The familiar cerebellopontine angle neurofibroma of the adult is also quite unusual in children. According to Craig, Dodge, and Ross[4] only two of 410 verified unilateral acoustic neurofibromas operated on at the Mayo Clinic between 1915 and 1953 occurred in patients under the age of 15 years. It would seem, therefore, that any tumor of the cerebellopontine angle is a rarity in childhood.

The likelihood that gliomas of the cerebellopontine angle occur more often than is commonly believed is suggested by the study of Svien and co-workers[8] dealing with the intracranial ependymomas observed at the Mayo Clinic. In their series of 126 intracranial ependymomas, 75 (59.5 per cent) were infratentorial; 70 occurred in the midline posterior fossa and five in the cerebellopontine angle. The majority of infratentorial ependymomas, they felt, arose from ependymal cells lining either the floor or the roof of the fourth ventricle and presented as midline tumors; they mentioned that ependymal cells of the lateral medullary velum might also give rise to ependymomas which could grow into the cerebellopontine angle. Spinal cord examination was made in ten cases, and in six instances of ependymoma within the fourth ventricle, spinal subarachnoid implantation was noted. Although it has been felt that the usual situation of intracranial ependymomas in the third or fourth ventricle favors the spread of desquamations or metastases into the adjoining subarachnoid spaces,[3] data in regard to such implants and metastases for ependymomas in the cerebellopontine angle are inadequate since the spinal cord was not examined in our case nor apparently in those reported by others.

The possibility of successful removal of cerebellopontine angle gliomas is suggested by their physical and pathologic character. Successful surgical treatment may have been effected in one such patient (case 9 of the Kernohan series); in this instance a six year old child was doing well three years after the enucleation of a large right cerebellopontine angle fibrous astrocytoma.

SUMMARY

1. The clinical and pathologic features of a papillary ependymoma of the cerebellopontine angle in a five week old male infant are described.

2. This child is believed to be the young-

est reported with a glioma of the cerebellopontine angle.

3. An associated developmental anomaly of the dorsolateral medulla oblongata occurred in this instance.

4. The tumor in our case resembled other reported gliomas of the cerebellopontine angle. In the majority, these have been ependymomas and are said to have had their origin in the lateral medullary velum (the floor and medial wall of the lateral recess of the fourth ventricle).

5. The physical and pathologic characteristics of gliomas of the cerebellopontine angle suggest the possibility of their successful surgical removal.

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■ Hyperæsthesia is also, but in a less degree, one of the results of a transversal incision in the cerebellum, in the processus cerebelli and testes, and in the tubercula quadrigemina.

If we carefully dissect the two restiform bodies so as to separate them from the neighboring parts, and if we divide them transversely at their two extremities, and then remove them, we find that the animal, instead of losing its sensibility, in the different parts of the limbs and trunk, becomes hyperæsthetic.

It results from these experiments, that the restiform bodies, which are the direct continuations of the posterior columns of the spinal cord, are not the only channels for the transmission of sensitive impressions to the sensorium.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

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FEBRUARY, 1956

Special Courses to Open AAN Meeting (April 23-28) The special review courses in graduate neurologic education, under the leadership of A. B. Baker, have been an annual highlight in Academy program activities. The 1956 special courses to be held in the Jefferson Hotel, St. Louis (April 23-25), backed by five years of development and experience, will present the most carefully planned program ever, on a wide range of requested topics.... On Monday, April 23, there will be an intensive review course in gross and microscopic neuropathology (Fae Y. Tichy, chairman), designed to reinforce the background in this field of clinical neurologists and other physicians wishing to gain theoretical knowledge. Two months prior to the course in neuropathology each applicant will receive a set of 100 specially prepared slides, together with instructions concerning methods of study, selected reading, and legends for the slides, so that each applicant will have an opportunity to review organized material well in advance of the course. Also on April 23, there will be a course on infectious diseases in neurology (Robert A. Utterback, chairman), emphasizing recent rapid developments in this field, both diagnostic and therapeutic, and their importance to the general practice of neurology.... On Monday and Tuesday, April 23 and 24, James L. O'Leary will present his popular lectures and demonstrations in the clinical and experimental aspects of modern neurophysiology, which now has been expanded to cover one and one-half days. In addition, on Tuesday, April 24, a course will be given on clinical electroencephalography and electromyography (Dewey K. Ziegler, chairman). This course will review the basic principles and clinical applications of EEG and EMG in health and disease, medicine and surgery, including instrumentation and recording technics, fundamental physiology and pharmacology, and normal standards for children and adults in waking and sleep. This course is directed toward clinical practice in neurology, psychiatry, neurologic surgery, and indications for use of EEG and EMG in general practice.... Also on Tuesday, April 24, a special course on convulsive disorders (Dave B. Ruskin, chairman) will present an up-to-date survey and digest of recent advances in all phases of diagnosis and treatment, both medical and surgical, of convulsive disorders. Particular emphasis will be placed on the more recent neurochemical applications to these disorders....

Also, on Tuesday, April 24, a new course will be given by J. Preston Robb on the neurologic disorders of infancy and childhood, designed to give a comprehensive survey of the field and point up the many neurologic problems and diseases in pediatric neurology which are not observed in the adult.... Another new course will be given Wednesday, April 25, in neurochemistry (Maynard M. Cohen, chairman), which will provide an intensive review and integration of the startling recent advances in this field, particularly those of importance to clinical neurologists. .... Also on Wednesday, April 25, there will be another new course on current advances in neurology (Joe R. Brown, chairman), presenting the current status on recent advances in such problems as control of pain, cerebral vascular disease, and radiation therapy in clinical neurology.... Finally, on the same day, Gilbert H. Glaser will give a course on injuries to the nervous system, which will survey the more recent concepts concerning cerebral concussion, edema, and contusion, as well as injuries to the spinal cord and peripheral nerves.... Fees for all courses except neuropathology are: fellows, actives, and associate members, $15.00; junior members, $10.00; non-members, $20.00. For neuropathology the fees are: fellows, actives, and associate members, $20.00; junior members, $15.00; non-members, $30.00; deposit on loan slide box: $25.00 (all member categories).... The number of registrants in each course will be limited and applications will be accepted in the order of their receipt. All applications and communications pertinent to the special courses should be forwarded to Mrs. J. C. McKinley, Executive Secretary, American Academy of Neurology, 3501 East 54th Street, Minneapolis 17, Minnesota.

Special Course for General Practitioners

In addition to this series of AAN special courses at the St. Louis meeting, a distinct innovation is the organization under Benjamin Boshes of a special course for general practitioners, Wednesday, April 25. Its purpose is to telescope newer developements in the diagnosis and treatment of common neurologic disorders into an intensive, one-day, practical presentation. Among the subjects to be covered are: headaches, strokes, parkinsonism, neurologic emergencies, disorders of muscle, and paraplegic states. Each subject will be discussed for not over one-half hour by a specially qualified AAN member; at the end of the session, a generous question and answer period will permit the course registrants to submit questions on the material presented or on any general neurologic topic. Answers to questions will be supplied by a hand-picked AAN panel.... Credit for the special course for general practitioners will be given by the American Academy of General Practice. Tuition for the course is $10.00, refundable to applicants who find they cannot attend by April 1, 1956. Applications and inquiries should be sent to Mrs. J. C. McKinley, AAN Executive Secretary, 3501 East 54th Street, Minneapolis 17, Minnesota.

Training Program at VAH, Oakland Walter F. Schaller, emeritus professor of neurology at Stanford University, announces the approval by the American Board of Psychiatry and Neurology of a two-year training program in neurology at the Veterans Administration Hospital in Oakland, California. VAH, Oakland, is a 712 bed general hospital, with 52 beds allocated to neurology. The full-time program director, J. K. Smith, is supported by a distinguished visiting staff: Walter F. Schaller, Knox Finley, and Leon Whitsell. For neurologic training as it pertains to women and children, residents may rotate through the Children's and Alameda County Hospitals in Oakland. At present there is one career resident under the program and a vacancy for one more.... Abundant research opportunities in neurology exist at VAH, Oakland; at present Bruno Gerstl, head of the pathology service, which also houses a biochemical laboratory, and J. K. Smith are conducting a project in multiple sclerosis under a grant from the National Multiple Sclerosis Society.... All inquiries or communications related to the program should be addressed to Dr. William R. Haas, Veterans Administration Hospital, Oakland, California.

* * * * * *

Arden House Conference on Neurological Disability On Dec. 5-7, in the quiet elegance of Arden House, formerly the Harriman country estate 48 miles up the Hudson River from New York City, a group of 50 leading neurologic scientists, health directors, and professional representatives from voluntary health agencies convened in the First National Conference on Neurological Disability as a National Problem. Under the auspices of the National Health Council and sponsored by United Cerebral Palsy, the conferees divided into five groups for a three-day session under general guide lines prepared by a planning committee headed by Dr. Glidden L. Brooks, medical director of United Cerebral Palsy. Under discussion were such problems as current programs of research and development, both government and private, what is being done for neurologic patients in all categories, the cost and the effects on the communities involved, and potential steps which could be taken to brighten the futures of those afflicted. Summarizing the conference, Mr. Leonard W. Mayo of New York, director of the Association for the Aid of Crippled Children, recommended that "a comprehensive total program of help be formulated and that it be presented to the American people, with a 'price tag' of the cost involved and the benefits which would accrue."... Recommendations for cooperative action in the five major areas discussed will be published later. Meanwhile, on Dec. 16, 1955, under a resolution adopted by the National Health Council's Board of Directors, the planning committee of the Arden House Conference will be continued as a permanent group appointed by the Council's president, Dr. Hugh R. Leavell of the Harvard School of Public Health.... The Arden House Conference grew out of a suggestion by Jack Hausman, the then president of United Cerebral Palsy.

ARNMD Elects New Officers Following its scientific sessions on the neurologic and psychiatric aspects of aging, the Association for Research in Nervous and Mental Disease at its thirty-fifth annual meeting (Hotel Roosevelt, New York, Dec. 9-10, 1955), elected Harry C. Solomon, president; Stanley Cobb and Wilder Penfield, vice-presidents; Rollo Masselink, secretary; and Lawrence C. Kolb, assistant secretary. H. Houston Merritt was elected member of the Board of Trustees; elected chairmen of the committees on admissions and public relations, respectively, were James H. Wall and Howard P. Rome.... Subject of the 1956 meeting of the ARNMD (Hotel Roosevelt, New York, December) is "Brain and Human Behavior."

Rose Re-elected Chairman of M.S. Medical Advisory Board At the semiannual meeting of the Medical Advisory Board of the National Multiple Sclerosis Society at the Biltmore Hotel, New York (Dec. 12), Augustus S. Rose, vice-president of the Academy, was re-elected chairman of the Board. Re-elected as vice-president was H. Houston Merritt, president-elect of the American Neurological Association. Announcement of these appointments was made by Ralph C. Glock, president of the Society.

Italian Neurological Society to Meet in Padova Prof. V. M. Buscaino, president of the Italian Neurological Society and honorary-corresponding member of the AAN, announces that the society will hold its Twelfth National Congress in Padova (April 4-6, 1956). Under an organizing committee headed by Prof. G. B. Belloni, the scientific sessions will center on two symposia: one related to modern developments in the field of encephalitis (relators: C. Berlucchi and V. Longo); the other devoted to the problems of epilepsy, its pathogenesis, relationship to the vegetative nervous system, and its medical treatment (relators: M. Gozzano, O. Maleci, and S. Rigotti, respectively).... for publication in the first volume of the congress, all abstracts and titles of presentations should be submitted to the Organizing Committee of the Congress, Neuropsychiatric Clinic, Padova, by February 1956.

Percival Bailey

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Dr. Volwiler also cited a Harvard Business school survey showing that, while industry generally spends about 1.2 per cent of sales on research, the drug industry spends somewhat more than 4.4 per cent. He appealed to educators in the audience to encourage young people with scientific aptitudes to train for careers in research. "Progress through drug research," he said, "could be speeded by the availability of increased numbers of young scientists. For the bright young man and woman studying science, increasing financial support is available. In chemistry, for example, the National Science foundation reports that 69 per cent of students majoring in this field receive some financial aid. Research on a broader scale is needed to make further progress against cancer, heart disease, hypertension, arthritis and the common cold. There are great opportunities for important discoveries and deep satisfactions for the young scientist."

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1. Proctor, R. C.: Report on Frenquel in acute and chronic psychotic states. Presented before the Bowman Gray Medical Society, Winston-Salem, North Carolina, May 16, 1955. 2. Rinaldi, F.; Rudy, L. H., and Himwich, H. E.: The use of Frenquel in the treatment of disturbed patients and psychoses of long duration, Am. J. Psychiat., in press. 3. Fabing, H. D.: Frenquel, a blocking agent against experimental LSD-25 and mescaline psychosis, Neurology 5:319, 1955. 4. Fabing, H. D.: New blocking agent against the development of LSD-25 psychosis, Science 121:208, 1955.

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